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CHICAGO NUMBER

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Correction

In an article entitled "Does Hyperglycemia Harm the Diabetic Patient?" which appeared in the Medical Clinics of North America for March 1947, in referring to a paper by Boyd, Jackson and Allen it was stated that "the degree of control of the disease was termed *good* if hyperglycemia was fairly constant and glycosuria frequent or continuous though mild" All who know the work of the Iowa group will recognize that they call this degree of control *poor*, and this is the word which was intended

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THE MEDICAL CLINICS of NORTH AMERICA

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SYMPOSIUM ON ADVANCES IN CLINICAL MEDICINE

FOREWORD

THE selections for this symposium have been made with the hope of bringing to the general practitioner the recent advances in the field of medicine most useful to him. Consequently such common and important conditions as hypertension, coronary disease, nephritis, peptic ulcer, the acute infectious diseases, the dysenteries, pneumonia and rheumatic fever are all discussed by competent authorities. The troublesome problem of chronic brucellosis is ably presented by Eisele. Less common, but equally important diseases such as bacterial meningitis, encephalitis, chronic hypoparathyroidism and disseminated lupus erythematoses are excellently considered by outstanding workers in the respective fields.

The electrocardiographic studies of Katz and Weinstein and the observations of Wakefield with regard to the association of gallbladder disease and heart disease will be read with interest, as will be the splendid discussion of steatorrhea by Ricketts and his associates. Two clinics are devoted to functional disturbances: one fascinating description by Dakin of the psychosomatic approach in general practice, and a more specific consideration of functional uterine bleeding by Davis. An up-to-the-minute consideration of the Rh factor is presented by Potter whose contributions in this field are well known.

The discussions of the recent developments in the use of the antibiotic drugs, including the adverse reactions, should be of particular interest to the general practitioner. Wagner's clinic on hay fever and asthma is based upon a broad experience with these conditions and includes a conservative evaluation of the new drug benadryl. The clinic on the action of radioactive phosphorus and the alkylamines in the treatment of neoplastic and allied diseases of the hemopoietic

system by Jacobson and his associates portrays a thrilling advance made during the war years

This volume is presented with the hope that it may be of immediate service to all practitioners of medicine

WALTER LINCOLN PALMER, M D

RADIOACTIVE PHOSPHORUS (P^{32}) AND ALKYLAMINES (NITROGEN MUSTARDS) IN THE TREATMENT OF NEOPLASTIC AND ALLIED DISEASES OF THE HEMOPOIETIC SYSTEM

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THE treatment of neoplastic diseases originating in the hemopoietic system with enteral or parenteral radioactive material has been employed only during the past decade. In fact, the only radioactive isotope that has been shown to be effective in such diseases is radioactive phosphorus (P^{32}), first used clinically by Lawrence and his associates¹. A recent exhaustive study by Reinhard, Moore and others² includes the review of the existing literature and an analysis of the use of radioactive phosphorus in the treatment of more than 150 patients with various blood dyscrasias. It is likely that with the advent of the "Atomic Age" radioactive isotopes for therapeutic purposes will be more readily available. Many investigators are directing their research toward a more specific attack on neoplastic tissue by means of attaching radioactive atoms to molecular structures which are differentially distributed to or taken up by neoplastic tissue. Knowledge of the metabolic behavior of phosphorus led early investigators to use radioactive phosphorus in the therapy of the lymphomas and leukemias¹. They showed that hemopoietic tissue and bone and neoplastic diseases originating therein took up a larger fraction of administered radioactive phosphorus than tissue such as muscle and brain.

Chemical agents have long been employed in treatment of various diseases of the hemopoietic system. Fowler's solution (potassium arsenite) was introduced in the latter part of the nineteenth century in the treatment of leukemia. More recently Forkner and Scott³ re-emphasized its usefulness as an adjunct to x-radiation. Benzol (C_6H_6) is still being used in European clinics primarily for the treatment of leukemia, but has been largely discontinued in this coun-

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try because of its toxic effects and complications. Phenylhydrazine still is used in the treatment of polycythemia rubra vera. Gilman and Philips,⁴ reviewing the biological actions and therapeutic applications of the alkylamines (nitrogen mustards), referred to the fact that two nitrogen mustards, namely tris (β -chloroethyl) amine and methyl bis (β -chloroethyl) amine had been used in the treatment of 150 patients by several groups of investigators^{5, 6, 7} In a preliminary report by Jacobson and his associates,⁸ the results of the treatment of fifty-five cases of leukemia, lymphoma or allied disorders with methyl bis (β -chloroethyl) amine hydrochloride⁹ were summarized.

It is the purpose of this communication to summarize briefly the clinical applications of radioactive phosphorus and methyl bis (β -chloroethyl) amine, and present cases illustrating the therapeutic effects of these totally differently acting agents on diseases of the blood-forming organs.

RADIOACTIVE PHOSPHORUS (P^{32})

In Table 1 is given the diseases of the hemopoietic system which we have treated with radioactive phosphorus.

Our own experience and that of a number of other investigators^{2, 9, 10, 11, 12, 13, 14} has been that radioactive phosphorus is probably the most effective agent available at present for the treatment of polycythemia rubra vera.

The effect of this isotope on the acute leukemias and multiple myelomas has been disappointing. The remissions produced in the treatment of Hodgkin's disease have likewise been unsatisfactory. Our results are corroborated in the publications of several other investigators^{2, 11, 12, 13, 15, 16, 17, 18}

The therapeutic response in chronic lymphatic and myelogenous leukemia has been largely comparable to that which is expected from x-radiation. Clinically significant remissions are usually produced also in lymphosarcoma after P^{32} administration but occasionally the results in individual cases are wholly unsatisfactory, as various communications indicate^{1, 2, 10, 11, 12, 13, 17, 18, 19, 20}

Method of Administration.—The reader is referred to the publications of various investigators^{1, 2, 12, 17, 18, 20} for the technical details of the preparation, administration and effective dosage of radioactive phosphorus in the treatment of the diseases listed in Table 1. Briefly, however, a sterile solution of radioactive phosphorus, such as the sodium acid phosphate, is administered orally or intravenously in single or divided doses. The effective dosage is highly individualized. In general multiple small doses each consisting of approximately 1 millicurie given intravenously are the most effective in the treat-

⁹ *Dema*, used hereafter for the sake of brevity

TABLE 1 --DISEASES TREATED WITH RADIOACTIVE PHOSPHORUS, DEMIA AND X RAY AND TYPE OF RESPONSE IN TERMS OF REMISSION

	Radioradiophosphorus (P^{32})	Length of Remission in Months	Bis (β -chloroethyl) methyl amine (Dema)	Length of Remission in Months	X radiation
Lymphatic leukemia -- acute	Unfavorable Favorable	0 3-12	Unfavorable Favorable	0 2-24	Unfavorable Favorable
Myelogenous leukemia -- acute	Unfavorable Favorable	0 3-12	Unfavorable Usually unfavorable	0 0-3	Unfavorable Favorable
chronic	Usually favorable	3-12	Usually favorable	1-10	Usually favorable
Lymphonarcosis	Usually unfavorable	0-8	Favorable Usually unfavorable	1-10	Favorable Usually unfavorable
Isodipkin's disease	None treated			$\frac{1}{2}$ -2 4-17*	Usually favorable Unfavorable
Sympathicoblastoma	Favorable Unfavorable	6-20+ 0	Favorable Unfavorable	0	Unfavorable

* All patients are still in remission.

ment of the leukemias and lymphomas. It must be emphasized that the isotope under discussion exerts varying effects on the hematological constituents of the peripheral blood, depending upon the disease being treated, individual sensitivity, and the amount of the isotope administered. Severe lymphopenia, neutropenia, thrombocytopenia and anemia may result if care and judgment are not exercised in each case. Frequent blood counts are essential in determining the effectiveness of the drug and in preventing these reactions.

In the treatment of *lymphomas* and *leukemias* we have found that approximately 1 millicurie may be administered intravenously once to twice weekly during the first two to three weeks of treatment. The frequency of injection is reduced or discontinued thereafter as indicated. The effect on the hematological constituents of the peripheral blood and clinical evidence of remission must serve as guides to the amounts and frequency of administration of the isotope in individual cases. If the isotope is administered orally, a 75 per cent absorption of the administered dose is assumed. It should be given preferably in the morning in orange juice. No breakfast should be given until at least two hours after the administration of the isotope. Milk and iron preparations should be avoided during the twenty-four-hour period preceding and following the administration of the isotope. These precautions are emphasized by several workers.^{2, 10, 20, 21, 22, 23}

In the treatment of *polycythemia rubra vera*, a single intravenous dose of 6 to 8 millicuries, or 8 to 10 millicuries by mouth, has usually produced a remission in our experience. In a few instances it has been necessary to repeat a dose largely comparable to the initial dose after three to five months. In order to avoid the complications of thrombosis in patients with high erythrocyte and hematocrit values at the onset of treatment, it is perhaps wise to do phlebotomies and reduce these values to approximately 6 million and 60 per cent respectively before, or concomitant with, the beginning of therapy with the isotope. Remissions of from six months to nearly two years, and even longer, have been produced in thirteen patients with polycythemia which we have treated thus far with P^{32} . The remissions produced in patients with polycythemia and reported by other investigators after the use of radioactive phosphorus vary in individual patients from six months to five years.^{2, 9, 10, 11, 12, 13, 14}

Illustrative Cases.—The following two case reports illustrate the effect of P^{32} on polycythemia rubra vera and lymphosarcoma respectively.

CASE I—Polycythemia Rubra Vera—W. B., a 43 year old coal merchant, was first seen at the University Medical Clinic on August 28, 1943 complaining of recurrent abdominal pain, nausea and vomiting, occasional dizziness, headaches and "flushed" feeling of two years' duration. Except for a florid complexion and an enlarged spleen, physical examination was essentially negative. Laboratory find-

ings revealed a normal urine, free acid on histamine test, negative Wassermann and Kahn reactions erythrocytes 6,500,000 per cu mm, hemoglobin 18.8 gm. per 100 cc. (photoelectric), leukocytes 11,400 with a normal differential, hematocrit reading 61 per cent.

The patient was hospitalized for study. X ray examination of the gastrointestinal tract revealed a deformity of the duodenal bulb with a crater. A blood count taken on admission was comparable to the first one made in the Out patient Clinic. Blood volume was measured using the Evans blue technic,²⁴ the results of which were total blood volume 6850 cc., red cell mass 4390 cc., plasma volume 2260 cc., hematocrit reading 66 per cent. The patient was placed on ulcer management and repeated phlebotomies reduced the red count to 5,300,000 per cu mm., the hemoglobin to 15.2 gm. per 100 cc., and the hematocrit reading to 50 per cent. He was discharged and seen at approximately monthly intervals in the Out patient Clinic. Phlebotomies were performed on the average of once monthly each time 500 to 600 cc. of blood was removed. He was maintained essentially symptom free on this regimen until October 1, 1943 when he noticed that the right side of his tongue and his right upper extremity felt numb, and a feeling like "needles and pins" appeared in the right arm. He also noticed short, fleeting episodes of a similar feeling in the right leg. The physical findings were compatible with cerebral thrombosis at the left posterior internal capsule.

Laboratory findings at this time revealed that the hematocrit reading had risen to 61 per cent and the erythrocytes to 6,500,000 per cu. mm. The patient was again hospitalized for a short period and phlebotomies were again performed on several successive days, reducing his hematocrit reading to 50 per cent and his red count to 5,400,000 per cu. mm. A more stringent ulcer management was instituted using alkalis, atropine and a low residue nonlaxative diet. By May 1944 the ulcer crater was no longer visible roentgenologically. The symptoms of polycythemia, including headache and dizziness, continued, however and in addition the patient complained of the persistent numbness and tingling and awkwardness of his right arm and leg. Frequent phlebotomies were still necessary and therefore beginning May 31, 1944 a series of intravenous injections of radioactive phosphorus, totaling 8.3 millicuries was given over a period of eight weeks. The initial injection of 3.3 millicuries was followed at intervals of two weeks by subsequent injections of 2, 1, 1 and 1 millicuries. Erythrocytes on the day of the initial injection numbered 6,500,000 per cu mm, hemoglobin 17.5 gm per 100 cc., hematocrit reading 62 per cent, platelets 285,000 per cu. mm, leukocytes 18,000 per cu mm.

Within eight weeks after the first injection the patient was free of headaches and dizzy spells and has remained in a symptomatic and hematological remission for more than seventeen months since the last injection, except for a mild residual awkwardness of the right arm and leg resulting from the original cerebral thrombosis. The duodenal ulcer has remained inactive symptomatically.

In Figure 1 is given the control and post-treatment effect of radio-phosphorus on the hematological constituents of the peripheral blood in Case I. The control value of each of the constituents represents an average of three samplings during the week prior to the first intravenous injection of 3.3 millicuries of P^{32} . One month after the last injection the patient's leukocytes numbered 3600 per cu mm. This leukopenia was largely a reflection of the reduction in neutrophils. The values of the other hematological measurements were at that time hemoglobin 14 gm. per 100 cc., erythrocytes 4,800,000 per cu.mm, platelets 155,000 per cu mm, hematocrit reading 40 per cent, and

reticuloocytes 1 per cent. The leukocyte value rose slowly thereafter as did the platelets and reticuloocytes. On the other hand, the hematocrit reading was further reduced to 34 per cent and the hemoglobin and erythrocyte values to 12 gm per 100 cc. and 3,400,000 per cu mm respectively before slowly rising to more normal values. Seventeen months after the last injection of radioactive phosphorus and nineteen

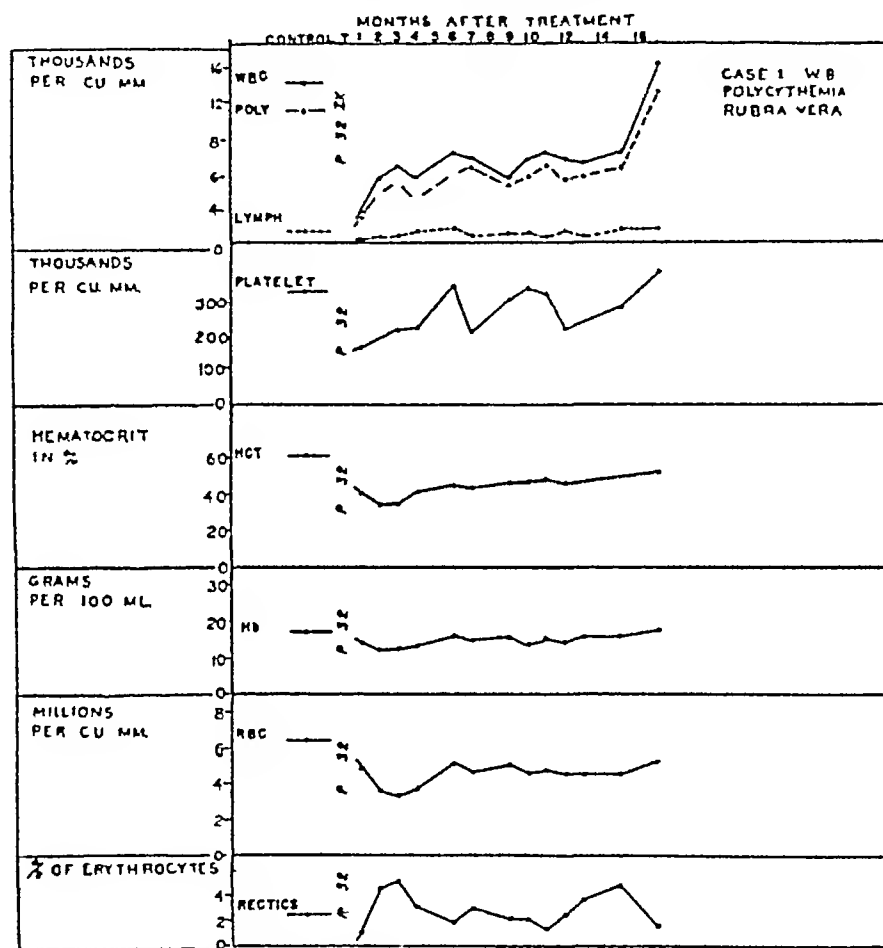


Fig 1 (Case I).—The effect of intravenously administered radioactive phosphorus on the hematological constituents of the peripheral blood of a patient with polycythemia rubra vera.

months after the first treatment with P^{32} , the hematological values of the peripheral blood are still within normal limits

The effects of these injections of radioactive phosphorus upon the peripheral blood illustrate the caution which must be used in the administration of this isotope. It is not unlikely that the last injection of 1 millicurie was unnecessary and perhaps this degree of anemia,

leukopenia and thrombocytopenia might have been avoided had it been omitted. It is also worthy of note that the mean corpuscular hemoglobin²⁵ rose to 35 micro-micrograms and the mean corpuscular volume to more than 115 cubic microns three months after treatment and gradually returned to normal thereafter. This has been noted in practically all patients who developed anemia following P³² therapy. It is

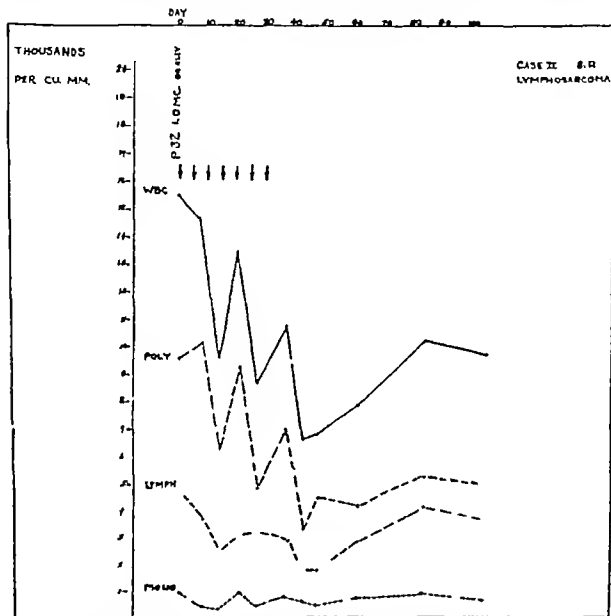


Fig 2 (Case II) —The effect of orally administered radioactive phosphorus on the hematological constituents of the peripheral blood of a patient with lymphosarcoma.

not due to an increase in reticulocytes. Macrocytes appear and the mean cell diameter rises concomitantly with this increase in cell volume.

CASE II —Lymphosarcoma.—S.R., aged 23 a housewife, was first seen in the Clinic on July 10 1945 complaining of increasing weakness and fatigue and enlarged lymph nodes in the neck area, axillae and groin. Approximately one year previously she noted the appearance of small masses in the neck and in the six months prior to her first visit she noticed the axillary and inguinal swellings.

Physical examination revealed a well developed woman in no acute distress, with anterior and posterior lymph nodes in the cervical region bilaterally, up to 15 mm in size, and bilateral axillary and inguinal nodes. The liver and spleen were palpable 1 cm below the costal margin on inspiration in the right and left midclavicular line respectively. The patient entered the hospital and a cervical node was removed surgically. Histological examination revealed a lymphosarcoma. The patient was discharged and beginning July 30, 1915 radioactive phosphorus therapy was begun. One millicurie of phosphorus was administered orally every five days until a total of 7 millicuries had been given. Within two weeks of the last dose the peripheral lymphadenopathy had disappeared except for several small, nontender 5 mm nodes in the posterior cervical chain bilaterally. The spleen and liver which had been palpable at the first admission were no longer palpable on inspiration and symptoms of weakness and fatigue were largely alleviated. In March 1946 the patient was symptom-free but the lymph nodes in the neck and axillae began to increase in size, and symptoms of malaise, weakness and fatigue recurred. A course of treatment with radiophosphorus, similar to that given previously, was repeated in April of 1946. Physical examination on June 11, 1946 revealed that the lymphadenopathy had again regressed.

In Figure 2 the effect of the first course of orally administered P^{32} on the leukocytes per cubic millimeter of the peripheral blood is shown. As is characteristically apparent after the administration of this isotope, the lymphocytes are reduced prior to the reduction of the neutrophils. The effect on the hemoglobin and erythrocyte values was negligible.

β -CHLOROETHYL AMINES (NITROGEN MUSTARDS)

Two alkylamine compounds have thus far been used clinically in the treatment of neoplastic diseases and allied disorders of the hemopoietic system. Our experience, which dates back to March 1943, has

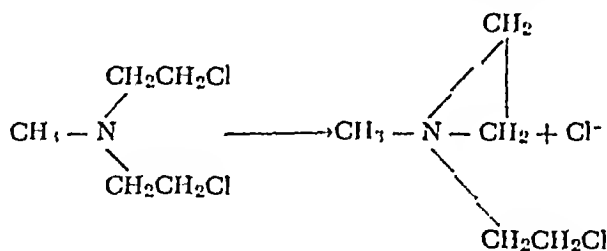


Fig 3—Formula of methyl bis (β -chloroethyl) amine hydrochloride and the first transformation product. The ethyleniminium derivative (shown on the right) is thought to be the physiologically active compound, according to Gilman and Philips.⁴

been confined to the use of bis methyl (β -chloroethyl) amine hydrochloride only.⁸ The formula for this drug and its first transformation product is shown in Figure 3. Other investigators have studied the effects of the tris (β -chloroethyl) amine hydrochloride as well.^{4, 6, 7}

Dema is dissolved in sterile normal saline and injected intravenously in a dose of 0.1 mg per kilogram of body weight for four successive

days Such a course of treatment is usually sufficient to produce a remission in Hodgkin's disease, lymphosarcoma, chronic lymphatic leukemia and polycythemia rubra vera The diseases with which we have had experience in the use of this drug are shown in Table 1 An attempt to compare the therapeutic effectiveness of Dema with P³² and x-radiation is also included in the table The remission produced thus in Hodgkin's disease (one to ten months), lymphosarcoma (one to ten months), lymphatic leukemia (two to twelve months), myelogenous leukemia (none to three months) are no longer, and perhaps shorter, than those which could be expected from x-radiation The remissions produced in polycythemia (four to seventeen months*) are significant It is quite definite, however, that the remissions produced in Hodgkin's disease with the alkylamines indicate its superiority over P³² in the treatment of this disease In our experience, remissions have been produced in cases of Hodgkin's disease and lymphosarcoma classified as x-ray resistant This drug has been ineffective in the treatment of the acute leukemias and multiple myeloma

The immediate toxic reactions are not serious and consist largely of nausea and vomiting within two to three hours after each injection The delayed and more serious reactions which may ensue are local thrombosis and thrombophlebitis, and destruction of hemopoietic tissue Thrombosis and thrombophlebitis are entirely avoided if the material is sufficiently dilute when administered

Lymphopenia, neutropenia and thrombocytopenia which develop with a course of four or more successive injections of the drug reach a maximum within the first three weeks The rapidity and severity with which these latter reactions are manifest depend upon the sensitivity of the individual to the drug, the disease concerned, and the total amount of drug given in a course With a course of four or more injections leukopenias of 2000 cells or less per cubic millimeter are common Anemia may develop but is usually minor Bleeding time may be increased but hemorrhagic manifestations are rare The changes occurring in the peripheral blood are paralleled in the bone marrow Serial sternal puncture and rib biopsies on selected patients following treatment indicate that an extreme destruction may occur Recovery of the bone marrow is complete after varying intervals and parallels the return of the constituents of the peripheral blood to normal limits

Illustrative Cases—The case reports of two patients treated with Dema are given below These cases, one of polycythemia rubra vera and the other of Hodgkin's disease, illustrate the therapeutic effect of the drug as well as its more serious toxic manifestations

CASE III.—Polycythemia Rubra Vera—S. L., a 38 year old discharged Navy seaman was first seen in the University Medical Center on August 4 1944, complaining of epigastric distress, palpitation, a dull upper abdominal pain, and

* All patients are still in remission.

nausea and vomiting of four months' duration. He had been told in 1938 that he had an enlarged spleen.

Physical examination was essentially negative except for a general ruddiness of the skin and an enlarged spleen, palpable 5 cm. below the costal margin. The blood pressure was 140 systolic and 94 diastolic. Laboratory examination revealed the following: leukocytes 18,200 per cu mm, hemoglobin 20 gm per 100 cc, erythrocytes 7,300,000 per cu mm, and an essentially normal differential count. The Wassermann and Kahn tests were negative.

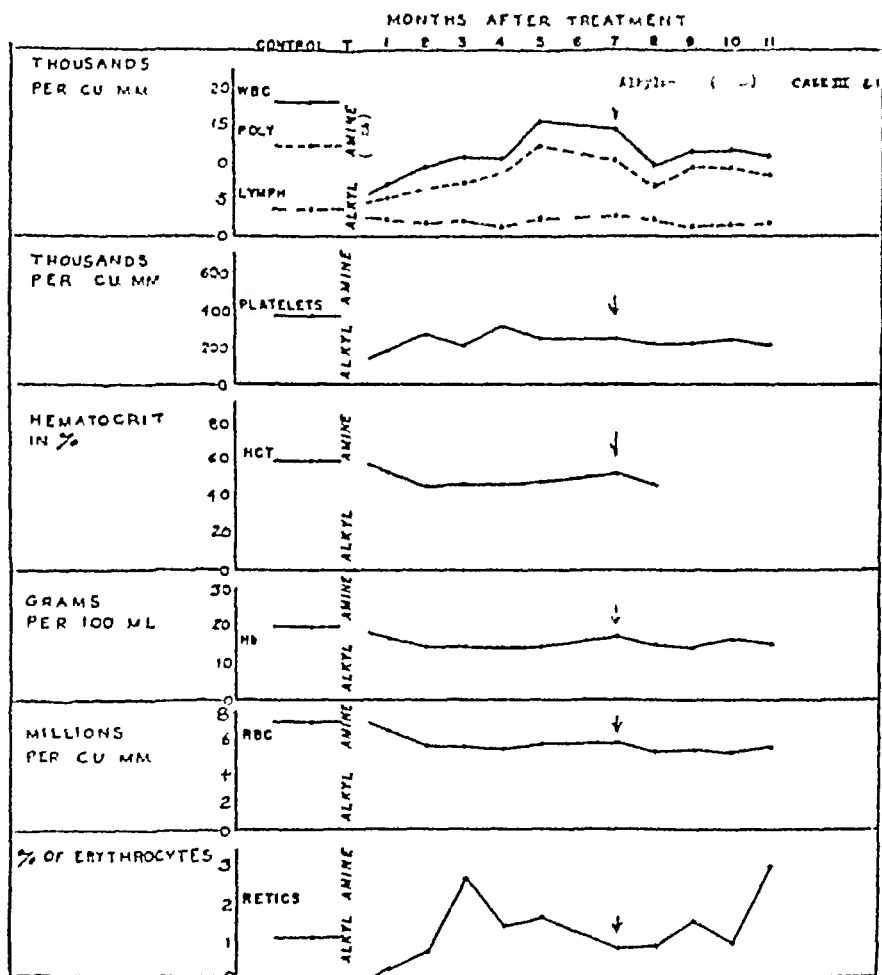


Fig 4 (Case III) -The effect of Dema on the hematological constituents of the peripheral blood of a patient with polycythemia rubra vera

The patient was hospitalized and the examinations conducted were indicative of a primary idiopathic polycythemia. Phlebotomies were done at frequent intervals in the Out-patient Clinic after his discharge and the cell volume was maintained at approximately 50 per cent for several months. The patient failed to return for phlebotomies between September 14, 1944 and January 1, 1945 at which time his cell volume had again risen to 64 per cent, hemoglobin 20.5 mg per 100

cc., erythrocytes 7,030,000 per cu. mm., and leukocytes 15,900 per gm cu. mm He was hospitalized on January 5, 1945

Beginning January 6, 1945 8.5 mg of Dema were given intravenously daily for four consecutive days Mild nausea and vomiting occurred within two to four hours after each injection. As is shown in Figure 4 the leukocytes were reduced from 18 000 to 4 000 cells per cu mm. within twenty-one days after the initial injection of Dema and rose gradually thereafter The hematocrit, hemoglobin and erythrocyte values fell to normal limits within a period of two months and have remained within normal limits over a period of seventeen months since the original treatment.

Seven months after the original treatment, the patient was again given a series of four daily injections of 8.3 mg. of Dema in the Out patient Clinic. Except for a slight reduction in the leukocytes and erythrocytes per cu mm. this series of injections had remarkably little effect compared to that noted after the first series of injections The patient remains under observation and is symptom free and still in remission from the hematological standpoint.

CASE IV—Hodgkins Disease—J. C., a 24 year old male clerk, was admitted to Billings Hospital on September 25 1944 On November 11, 1943 the patient had been hospitalized elsewhere because of epigastric distress of a years duration

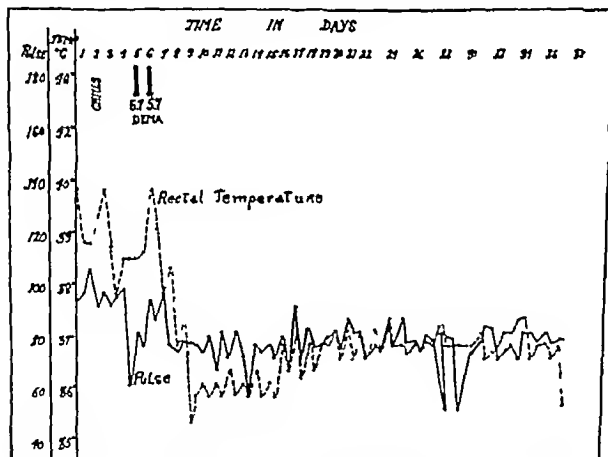


Fig 5 (Case IV) —The effect of a course of Dema upon the temperature and pulse of a case of Hodgkins disease

tion and the discovery of lumps in his neck. A biopsy of a cervical lymph node made at that time was reported to the patient to show Hodgkins disease In December of 1943, a series of eight x ray treatments were given to the neck, five to the right axilla and ten to the abdomen and back, with relief of symptoms and decrease in the size of the lymph nodes. In approximately two months however,

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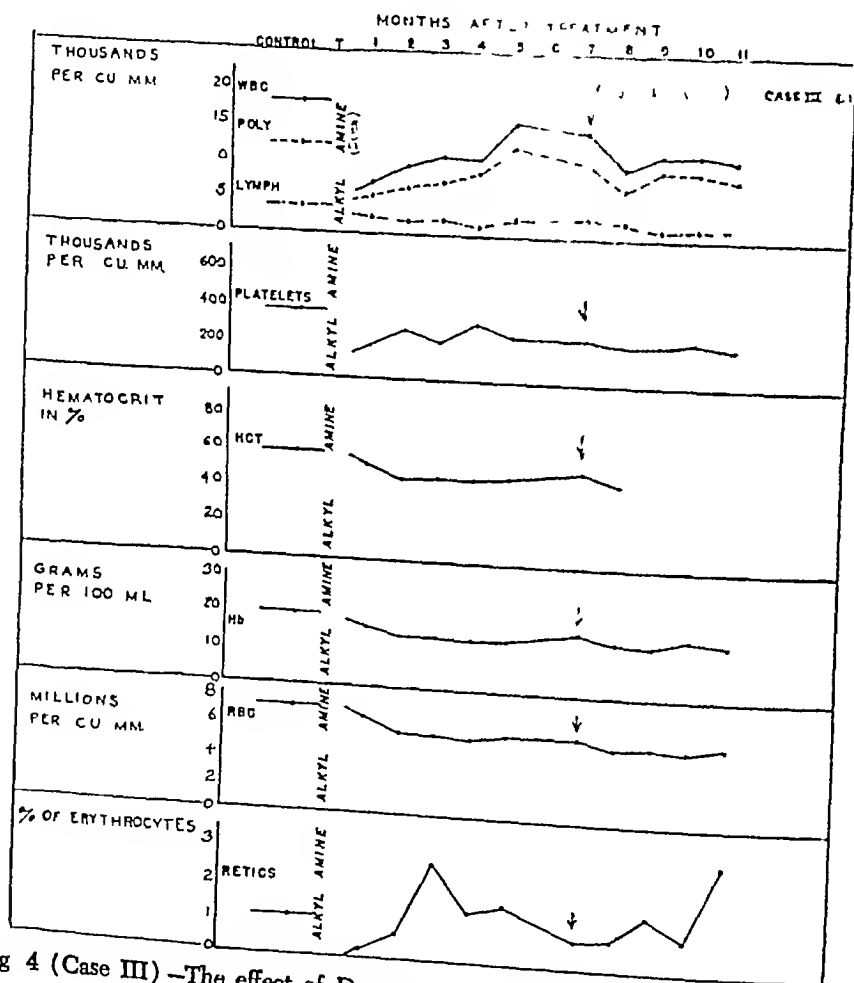


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The patient was hospitalized and the examinations conducted were indicative of a primary idiopathic polycythemia. Phlebotomies were done at frequent intervals in the Out-patient Clinic after his discharge and the cell volume was maintained at approximately 50 per cent for several months. The patient failed to return for phlebotomies between September 14, 1944 and January 1, 1945 at which time his cell volume had again risen to 64 per cent, hemoglobin 20.5 mg. per 100

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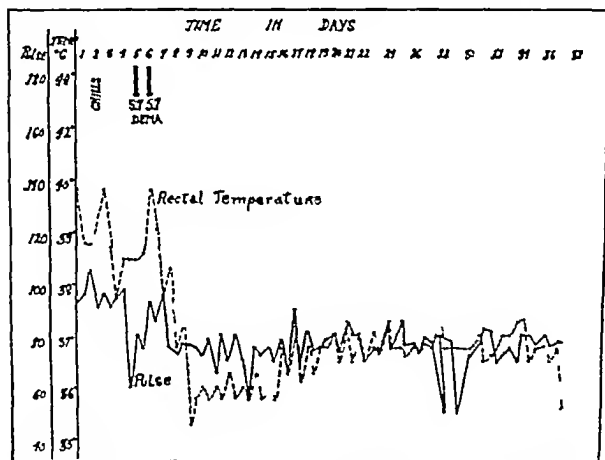


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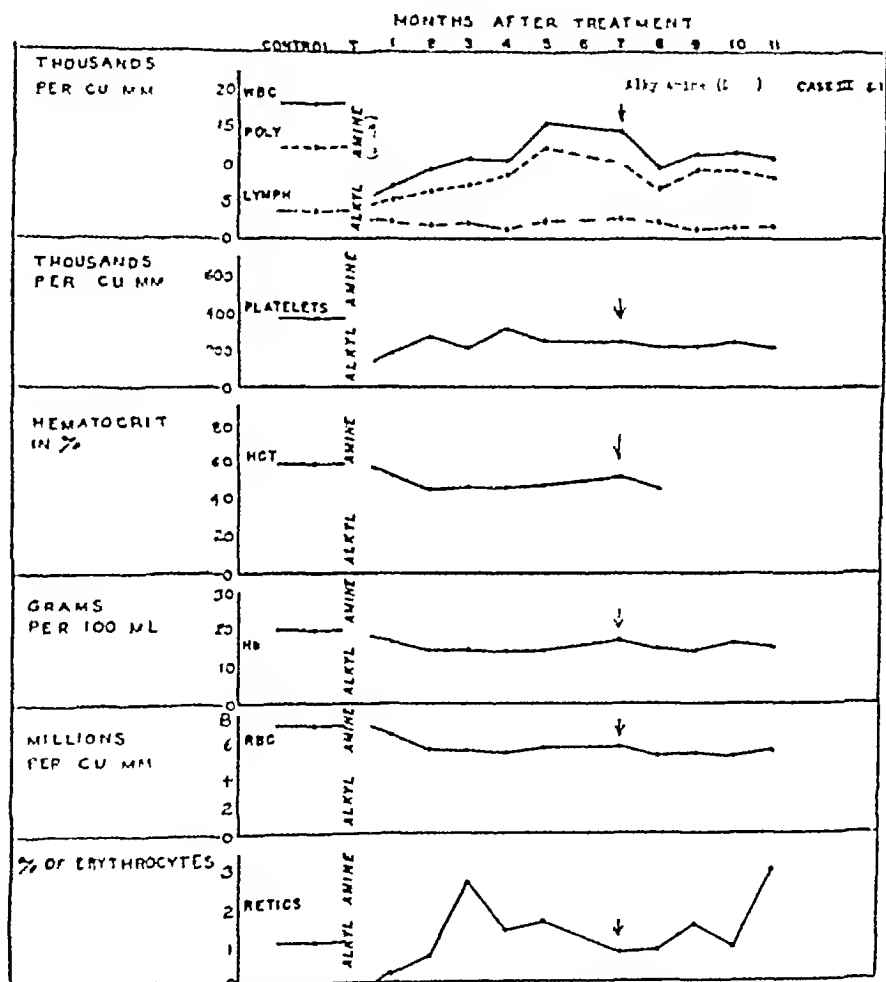


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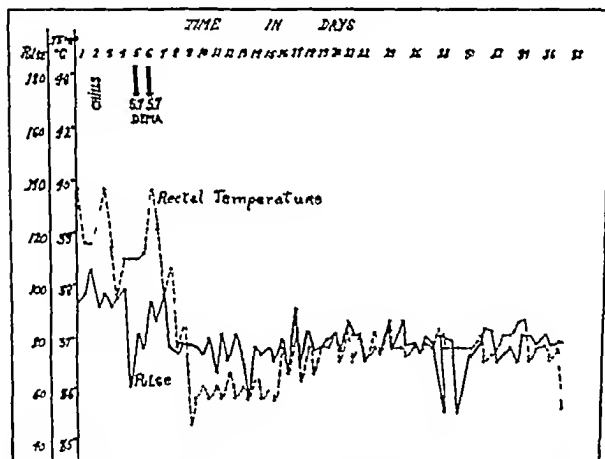


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the patient's original complaints recurred and in addition he noted increasing weakness and fatigue. In May 1944 he began to have recurrent chills and fever.

On examination the patient was found to have a temperature of 40°C , pulse 100, cervical lymphadenopathy, hepatomegaly and an anemia. Study of the peripheral blood revealed hemoglobin 8.9 gm per 100 cc (photoelectric), erythrocytes 3,340,000 per cu mm, platelets 14,000 per cu mm, leukocytes 2,100 per cu mm, a prolonged bleeding and clot retraction time, normal clotting time and increased capillary fragility (Rumpel-Leede). The Wassermann and Kahn tests were negative. Examination of the original biopsy specimen revealed typical Hodgkin's disease.

In view of the leukopenia and thrombocytopenia, it was decided to give the patient only two injections of Dema and on October 1 and 2 a dose of 5.7 mg was injected intravenously. Mild nausea and vomiting followed each injection within three hours. As is shown in Figure 5, the patient's temperature fell to normal within forty-eight hours after the first injection. This is a characteristic response to Dema in the treatment of Hodgkin's disease. Five days after the initial injection the leukocytes of the peripheral blood had fallen to 875 per cu mm, of which 744 were neutrophils and 96 lymphocytes. The platelets, however, had risen to 82,000 per cu mm. Ten days after the initial injection the leukocyte and platelet values reached 2000 and 100,000 per cu mm respectively, and the bleeding and clot retraction time were within normal limits. Within forty-eight hours after the first injection the patient felt well and within three weeks the lymphadenopathy and hepatomegaly had resolved. The remission produced by this first course of two injections lasted four months. The patient has since received seven courses of therapy with Dema, each consisting of four consecutive daily injections of 0.1 mg per kilogram of body weight. Remissions have been from two to five months' duration. The lymphadenopathy and hepatomegaly have not recurred since the original treatment. Remissions are terminated by appearance of chills and fever, malaise or leukopenia and thrombocytopenia, or as has been true on three occasions by presentation of generalized petechiae of the skin and mucous membranes and bleeding gums with or without accompanying chills and fever. Platelet values before treatment in these instances have been between 30,000 and 40,000 per cu mm with a prolonged bleeding and clot reaction time. A course of therapy with Dema has been followed promptly by cessation of symptoms, chills and fever, disappearance of petechiae, a return of bleeding and clot retraction time to normal, and a rise in the platelet value to 100,000 per cu mm or more. The leukocyte values, which before each course of therapy usually are between 1800 and 3000 cells per cu mm, rise slowly with the induced remission to approximately 4000 per cu mm.

Figure 6 illustrates the effect of a course of therapy with Dema on the constituents of the peripheral blood. A moderate immediate reduction in the leukocytes occurred but rose thereafter to a value higher than that which existed before treatment was given. The platelets likewise rose considerably following treatment. It is interesting to note that these values fell again before an exacerbation of malaise, chills and fever recurred. These effects have been duplicated largely with each course of therapy except the immediate leukopenia occurring within five days of the initial injection is usually more severe than occurs after this particular course of treatment.

The patient returned to work shortly after the first course of treatment in 1944 and except for the periods of exacerbation of his symp-

toms and the time off for treatment, remains employed. The patient was hospitalized for the first two courses of treatment. The six courses since have all been administered in the Out-patient Clinic

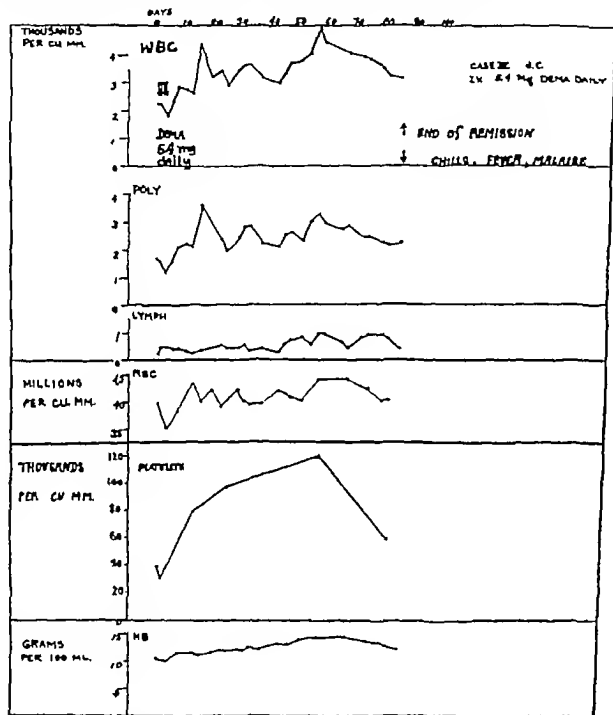


Fig 6 (Case IV) —Graph of the hematological constituents of the peripheral blood showing the effect of a course of Dema on an existing leukopenia, neutropenia, thrombocytopenia and anemia in a patient with Hodgkin's disease

SUMMARY AND CONCLUSIONS

Radiophosphorus and methyl bis (β -chloroethyl) amine hydrochloride in the treatment of neoplastic diseases of the hemopoietic system like x-radiation, have definite limitations. The course of the acute leukemias and multiple myeloma is unaffected by treatment

with these agents. Radiophosphorus usually does not favorably influence the course of Hodgkin's disease while Dema and x-radiation produce definite remissions. More or less comparable remissions are produced in chronic myelogenous leukemia by the administration of P^{32} and x-radiation, while Dema produces only a short or wholly unsatisfactory clinical response. The three agents are roughly equivalent in therapeutic efficacy in the treatment of lymphosarcoma. Radiophosphorus induces satisfactory remissions in polycythemia rubra vera with regularity. Observations on patients with polycythemia rubra vera after treatment with Dema are not long nor extensive enough to permit a logical comparison with the results obtained with P^{32} in the treatment of this disease. Dema has produced clinically significant remissions in the few patients treated thus far however.

Radiophosphorus is effective in the diseases discussed when given orally or intravenously. If given by mouth it should be administered in orange juice in the morning and breakfast omitted or postponed for at least two to three hours. A 75 per cent absorption should be assumed when given orally. The effective and "safe" dose or dosage schedule is highly individualized. The possible serious toxic reactions of the isotope are leukopenia, thrombocytopenia and anemia.

The dose of Dema in the diseases in which a trial is indicated is usually 0.1 mg per kilogram of body weight per day intravenously for four consecutive days. In individual cases a shorter or longer course of therapy may be indicated. The serious toxic manifestations of Dema which may ensue are (1) nausea and vomiting two to three hours after administration of the drug, (2) thrombophlebitis and thrombosis at the site of injection if the material is not sufficiently dilute when given intravenously, and (3) leukopenia, thrombocytopenia and anemia.

The case histories of four patients are presented to illustrate the therapeutic effect and some toxic manifestations of P^{32} and Dema. In Cases I and II, of polycythemia rubra vera and lymphosarcoma respectively, P^{32} was given. Dema was given intravenously in Cases III and IV. Case III was one of polycythemia rubra vera, and Case IV a severe case of Hodgkin's disease.

Although experience with Dema and related compounds is accumulating, the number of cases studied is too small and the period of observation too short to present a proper evaluation of their therapeutic efficacy at this time. It would appear, however, that Dema is a useful adjunct to the other agents in the treatment of certain neoplastic diseases of the hemopoietic system. Radiophosphorus has been adequately shown to have a place in the treatment of such diseases and particularly in the treatment of polycythemia rubra vera.

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RECENT DEVELOPMENTS IN THE USE OF THE ANTIBIOTIC DRUGS

GUSTAVE FREEMAN, M D °

DURING the past several years we have become acquainted with the application of penicillin and streptomycin in specific infections through tests in the laboratory, their use in the military services and in many civilian clinics. Although we may be fairly well practiced and informed in the use of penicillin and less so with streptomycin, much remains to be learned. Now the increased availability of penicillin leads us to treat conditions with fever that are not clearly defined but demand a trial of antibiotics for want of other efficacious measures of attack.

The following group of cases represents some such conditions for appraisal. First, however, will be described a case of subacute bacterial endocarditis and its treatment to provide contrast with the other less well defined diseases, from the point of view of diagnosis and treatment.

CASE I SUBACUTE BACTERIAL ENDOCARDITIS YIELDING TO LARGE DOSES OF PENICILLIN AFTER FAILURE OF SMALLER DOSES

G J O'S came to this clinic with the following story. At the age of 12 he spent six months in bed with "heart trouble" and swollen feet. He did not recall having had painful or swollen joints. He has had no other attacks suggestive of rheumatic fever.

In November 1944, at the age of 26, he had three teeth extracted. About two months later there was noticeable deterioration of strength. Four months after the extraction of teeth he experienced sudden loss of control of his right hand. He felt dizzy and some hours later was found disoriented, perspiring and with limpness of the right arm. At first a diagnosis of meningitis was made but soon was changed when it was learned that he had a "bad heart."

In a hospital he received 20 000 units of penicillin five times daily (100 000 per day) for three weeks but continued to have fever. The use of his arm returned. He was "given up as hopeless" and allowed to rest at home. Within a few weeks he developed an irritative, nonproductive cough and was admitted to this clinic.

This 27 year old white man appeared feverish. His skin was moist and warm but no petechiae or other embolic phenomena were visible. His temperature and pulse were elevated. The blood pressure was 120/40. The heart appeared to be enlarged. The precordium was visibly disturbed by the cardiac rhythm which was regular at 100 beats per minute. The second pulmonic sound was loud and snapping. Systolic and diastolic murmurs were audible at the apex and the base of the heart except for the absence of a diastolic murmur over the aortic area. The spleen was not felt although there was tenderness in the area.

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The leukocyte count was not elevated. The erythrocyte level was moderately low as was the hemoglobin. The urine contained red cells and occasional casts. Arterial and venous blood cultures were found to contain streptococci of the non-hemolytic, non-green forming type in small numbers. A nose and throat culture did not reveal hemolytic streptococci.

Figure 7 demonstrates the daily high and low points on the temperature curve during the first two weeks of hospitalization, the results of blood cultures and the dosage of penicillin.

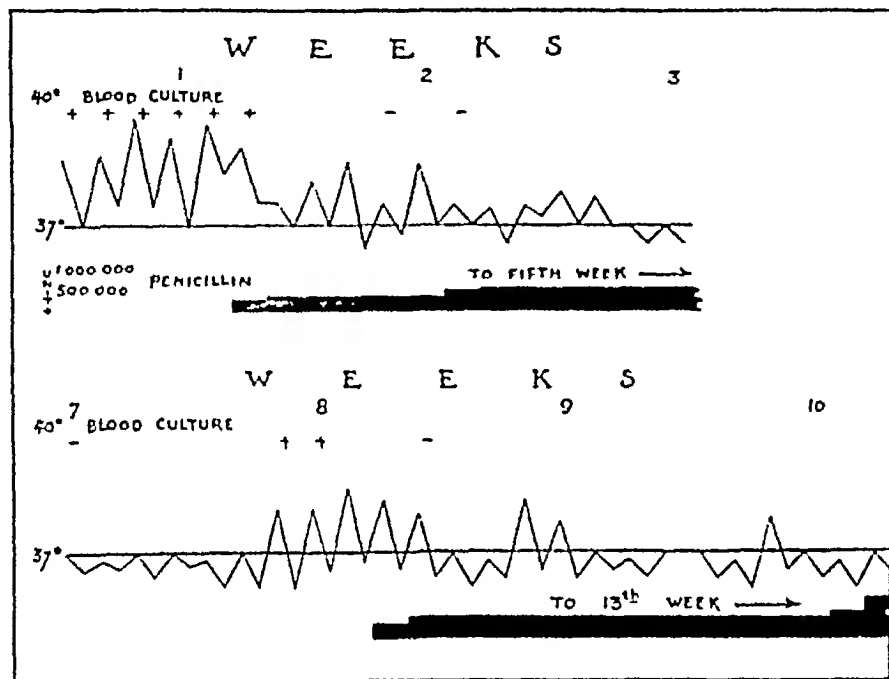


Fig 7—Recurrence of positive blood culture during eighth week in Case I after low dosage of penicillin and successful use of high dosage subsequently.

In Table 1 can be seen the patient's progress according to the penicillin received in this clinic.

It is apparent that the 100,000 units of penicillin daily that were given originally did not affect the course of the disease perceptibly and the case was abandoned as being resistant to antibiotic therapy. Neither did 480,000 units for three weeks completely destroy the reproductive capacity of the streptococcus in spite of a relatively low concentration of bacteria in the blood stream. However, 960,000 units over a minimum period of four weeks completely inhibited reproduction of the streptococci so that forty weeks later the patient was at work and still feeling well. In order to avoid overtaxing the myocardium, it was advised that a sedentary occupation be followed.

If the two unsuccessful series of treatments with low doses of penicillin did increase the resistance of the streptococcus to that antibiotic,

it apparently did not prove to be a serious obstacle. It is generally conceded now that approximately 1,000,000 units of penicillin is the dose of choice in treating bacterial endocarditis^{1 2}. There seems to be no benefit in using anticoagulants together with penicillin in this

TABLE 1 —CLINICAL PROGRESS OF THE PATIENT UNDER PENICILLIN THERAPY

Week	Fever	Blood Culture	Penicillin Units Daily	Clinical Changes
1	High	Pos (6)*	Started	Temperature fell.
2	Moderate	Neg (2)	320,000	Bed rest.
3	0	Neg. (1)	480,000	Afebrile
4	Slight (2)*	—	480 000	Abdominal pain.
5	0	Neg (2)	Stopped	Stiff neck.
6	Slight (1)	Neg (1)	—	—
7	0	Neg. (2)	—	Sitting up
8	Moderate	Neg (1)	Started	Fever again. Bed rest.
		Pos. (2)		B.P. 140/0
9	Moderate	Neg (1)	480 000	B.P. 136/50
10	Slight (2)	—	960,000	—
11	0	Neg (1)	960,000	—
12	0	—	960,000	—
13	0	—	960,000	—
14	0	Neg. (1)	—	—
15	Slight (1)	Neg (1)	—	Sitting up
16	0	Neg (2)	—	More activity
17	0	Neg. (1)	—	—
18	0	Neg (2)	—	Discharged.
23	0	Neg (1)	—	Apical systolic aortic diastolic, B.P. 154/54
30	0	—	—	Feels well. Return to work.
35	0	Neg (1)	—	Working as elevator operator WBC normal, Hb 15.9, RBC 5 080,000
39	0	—	—	Well. B.P. 130/80 Blood streaking on blowing nose.
43	0	—	—	Urine clear Well.
54	0	—	—	B.P. 152/56 Well. Gaining strength.

* Figures in parentheses refer to the number of times in the week this result was obtained.

disease. On the contrary, there is evidence that interference with the tendency for thrombus formation over damaged endocardial surfaces may encourage embolism³.

CASE II OBSCURE PNEUMONIA, PROBABLY ATYPICAL, IN WHICH PENICILLIN WAS USED AGAINST SECONDARY INFECTION

In the second case the problem of penicillin therapy arose in the treatment of K. S. a 25 year old Japanese-American with pneumonia who apparently did not respond to penicillin therapy at home and came to this clinic for further care.

The patient had a respiratory infection five months prior to the present attack. He had low grade fever, night sweats and pain in the left side of the chest for twelve days. An x-ray revealed no lesion. He recovered and was well until May 8, 1946.

At that time he noticed fatigue for two days which was followed by a rise in temperature to 103.8°F , a cough and pain in the left chest. He also had severe headaches continuously. After three days of fever he was treated with 50,000 units of penicillin every three hours for four injections and then by 30,000 units every three hours for a week. The pain decreased but he perspired profusely and felt "full" in the left side of the chest. He produced a small amount of blood-tinged sputum. For two days he had difficulty in passing his urine although the desire was present.

On the patient's admission to the hospital the base of the left side of the chest was dull and breath sounds were not audible over that area. They were heard with increasing clarity higher in the chest. Râles were heard in the upper portion. The heart rate was little increased although the temperature was 40°C (104°F). This relative bradycardia persisted throughout the course of the disease. A thoracentesis produced 1200 cc of "clear fluid" in which 98 per cent of the cells were mononuclear.

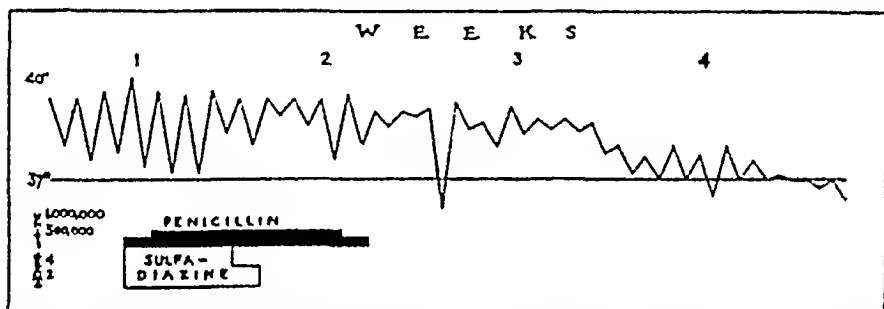


Fig 8—Failure of pulmonary infection to respond to penicillin and sulfadiazine followed by spontaneous resolution

At the time of admission 10,150 leukocytes per cu mm with 75 per cent polymorphonuclear cells were counted in the blood. The following day and for the next four weeks the leukocytes ranged from 5900 to 7500 cells. During the first few days the centrifuged urine contained a few leukocytes and an occasional cast. Stools were not unusual.

Sputum was studied repeatedly by smear and culture for aerobic and anaerobic bacteria, fungi and acid-fast organisms with negative results. Mice were inoculated intranasally and mice and guinea pigs intraperitoneally with sputum but the animals showed no evidence of disease. Agglutination tests were done early and in convalescence with live and dead typhoid bacilli, *B. proteus* OX 19, paratyphoid bacilli A and B, *B. tularensis*, and *Brucella* antigens. All were negative or insignificant in titer. "Cold" agglutinins were not demonstrable either early or late in the disease. Blood and nose and throat cultures on admission produced no significant organisms. Pleural fluid gave negative results on culture.

Penicillin was used for a week prior to admission. Figure 8 shows the temperature curve observed following admission as penicillin and sulfadiazine were tried. The former was administered in a dosage of 480,000 units daily for nine days and the latter for five days.

X-rays revealed pleural effusion in decreasing amounts as the patient improved and fluid was withdrawn. After fever had subsided an x-ray showed some residual pneumonitis in the lung. Those findings and night sweats persisted for several weeks after the temperature fell to normal.

The history and clinical and laboratory findings did not offer a clear concept of a specific pulmonary disease. The previous episode of fever and pain in the left side of the chest together with night sweats and the present attack with pleural effusion suggested an acute flare-up of tuberculosis. The failure of penicillin to alter its course was in favor of that impression. On the other hand the lack of leukocytosis, the severe headache and failure in response to the antibiotic suggested a nonbacterial pneumonia.⁴ The eventual failure to demonstrate "cold" agglutinins was not in favor of that diagnosis but did not eliminate it. Pleural effusion is uncommon in uncomplicated "atypical" pneumonia. The patient was a lathe worker in Chicago and had never been in areas known to be endemic for coccidioidomycosis. He was not aware of having been in contact for months before his illness with anyone who had a noticeable respiratory infection and he had no direct contact with pigeons or other birds known to be carriers of ornithosis virus. There were flocks of pigeons, however, in the neighborhood of his home. He was not in the habit of feeding them or observing them at close range.

The patient's relatively rapid recovery and negative sputum examinations for acid fast bacilli strongly suggest that the tubercle bacillus was not the cause of his disease although such a conclusion could not be established with finality. The inability to isolate bacteria or fungi suggests that they were not responsible primarily for the disease.

The opinion prevailed finally that the underlying disease was an atypical, nonbacterial pneumonia based on the finding of an unchanged leukocyte level, headache, failure to respond to penicillin and sulfadiazine, the relatively low heart rate and the negative results in the search for known agents of pulmonary infection. The history of a previous milder attack and the pleural effusion were indicative of a complicating bacterial infection that probably was held in control by therapy. However, it cannot be said that pleural fluid, particularly with a great predominance of mononuclear cells, could not have been part of a nonbacterial disease.

Unless a maximum dose of penicillin is employed, it is not certain that the failure of pneumonia to respond to penicillin means that the causative agent is one known to be resistant. However, from experience gathered in treating pneumonia, it is fair to assume that such is the case after employment of doses used here. In retrospect, the absence of an obvious epidemic of atypical, nonbacterial pneumonia and the unusual pleural effusion was adequate cause for trial of penicillin in spite of the inability to recover a causative agent of recognized susceptibility to the drug.

CASE III. UTILIZATION OF ANTIBIOTICS AS A PREVENTIVE MEASURE AGAINST POSTEMBOLIC PULMONARY INFECTION

Mrs. L. L. is a 49 year old woman who recalled having had aches and pains in her legs as a child of 13 although she was not put to bed. She had frequent sore throats and two tonsillectomies, the second at the age of 23.

When she was 37, she experienced a period of fatigue during which time there were paresthesias in her limbs and occasional nausea, dizziness and blurred vision. The following year she was hospitalized at this clinic for similar complaints and was found to have slight facial weakness on the right and some deviation of the tongue to the left on protrusion. The second heart sound over the pulmonary area was more distinct and snapping than that over the aortic and a diastolic murmur was heard over the mitral area. The blood pressure was 100 (systolic) and 52 (diastolic). Laboratory data including an electrocardiogram was normal. She was discharged shortly free of symptoms and abnormal signs.

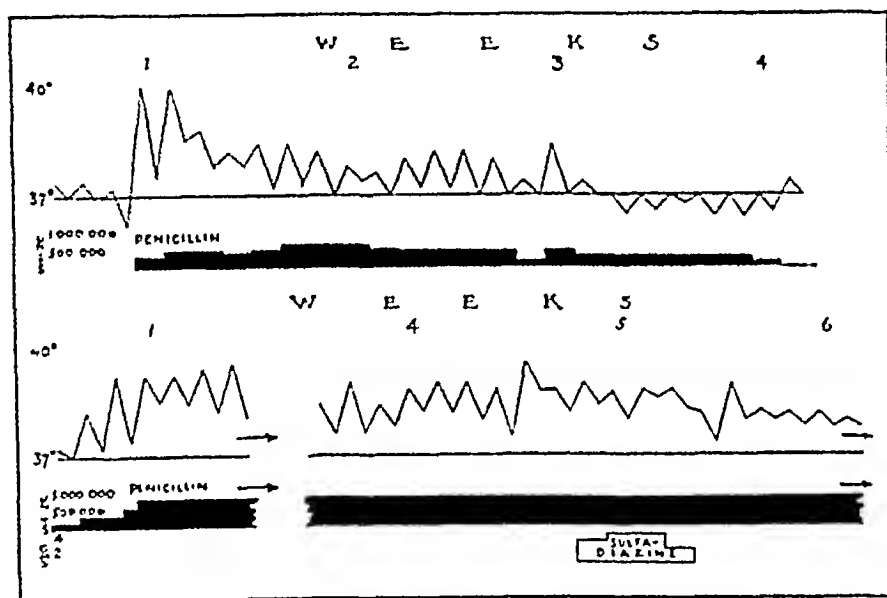


Fig. 9—Preventive use of penicillin in multiple pulmonary infarction

The patient carried on an unusually active career during the following seven years and then at the age of 45 suffered an acute right-sided paralysis with unconsciousness lasting twenty-one days. She recovered to a considerable degree and was hospitalized here for evaluation and speech training since the cerebral accident had left her with considerable aphasia. Her heart was enlarged but the rhythm and rate were normal. The blood pressure was normal and an electrocardiogram revealed "auricular abnormality." Other laboratory tests were within normal limits and she was discharged with a diagnosis of embolism to the left lenticulostriate artery from a left auricular thrombus.

During the next two years the patient had several teeth extracted. This occasioned nausea, vomiting and palpitation for two days. Similar attacks came on during the ensuing months and the patient was hospitalized during one such episode. Systolic and diastolic murmurs were apparent and the rhythm of the heart was disturbed by extrasystoles. Except for the latter, the electrocardiogram revealed no change. She was discharged in November 1944.

In April, 1946 the patient was readmitted after having had palpitation for two weeks. The heart rhythm was regular at a rate of 150 to 160 per minute. Since the heart was not adequately under the influence of digitalis although it had been taken at home irregularly, digitalization was carried out.

On the fourth day of hospitalization, as seen in Fig 9 there was a sudden onset of fever with pain in the chest and respiratory distress. The leukocyte count jumped from 8250 to 23 000 cells per cu. mm. The patient received penicillin for twenty two days. Pleural and pericardial effusions which followed the acute pulmonary embolism subsided but the cardiac fibrillation which began at the same time persisted. The heart was considerably enlarged and showed deterioration by electrocardiogram.

The patient was discharged after the chest had cleared but had a recurrence of low grade fever during the week at home. She was readmitted and penicillin and digitalis were reinstituted. Multiple small fluid levels were demonstrated by x ray. Penicillin was given continuously for one month and the temperature finally began to fall. Blood and pleural fluid cultures were negative on several occasions.

The patient described here is one who has either had cerebral thrombosis on the basis of local rheumatic vascular lesions several years ago or a long series of embolic phenomena from the left side of a rheumatic heart followed by pulmonary emboli from the right side during the two latter periods of hospitalization.

The attacks of palpitation, nausea and vomiting following extraction of teeth suggest that bacteria were released as a result of that procedure which commonly has been found associated with bacterial endocarditis in rheumatic hearts. It appears that possible infection from that source did not persist as an endocarditis but stresses the constant danger of serious bacteremia in such persons.

Although pulmonary infarction is likely to produce fever it is not always accompanied by infectious pneumonitis. However, in this case as well as in less debilitated individuals, preventive therapy should be instituted immediately to avoid or minimize infection of infarcted areas. It would appear unlikely that this 49 year old woman could have survived multiple pulmonary infarction and subsequent widespread pneumonitis without massive penicillin therapy throughout the period of healing of the lungs.

It is interesting to note that pulmonary embolism occurred soon after digitalization was pressed, suggesting that a change in cardiac rhythm or contractile power may have aided in releasing thrombus from the auricular endocardium.

CASE IV INTRACTABLE POSTPARTUM URINARY INFECTION AND THROMBOPHLEBITIS YIELDING TO STREPTOMYCIN AFTER FAILURE OF PENICILLIN AND SULFONAMIDES

Mrs. M. K., 42 years of age gave birth sixteen months prior to her admission. Since parturition she has had pain in the left groin. This persisted for fourteen months and was followed by swelling of the left leg. After two months of ineffective treatment at home she came to the hospital. Her leg was swollen and firm, tender inguinal lymph nodes were observed. Her temperature was 35 C. (100.4 F.)

During the first week she was given sulfadiazine and the temperature gradually fell to normal (Fig 10). The following day she had a chill as her temperature rose to 39°C (102.2°F). She had pain over the left kidney and many leukocytes were seen in her urine. A culture, however, showed no growth. The sulfadiazine was stopped and penicillin was given for the next two weeks. Although the temperature responded for the first few days, it soared again to 38.8°C (101.8°F). This was accompanied by low pleural pain and referred shoulder pain. An x-ray corroborated the findings of an infaret or embolic pneumonitis in the base of the left lung. Sulfadiazine was given again together with the penicillin. At this time the urine culture was positive for *B. Coli*.

The urinary cultures were positive persistently for the next two months although the temperature fell and hovered close to normal. Although the penicillin was

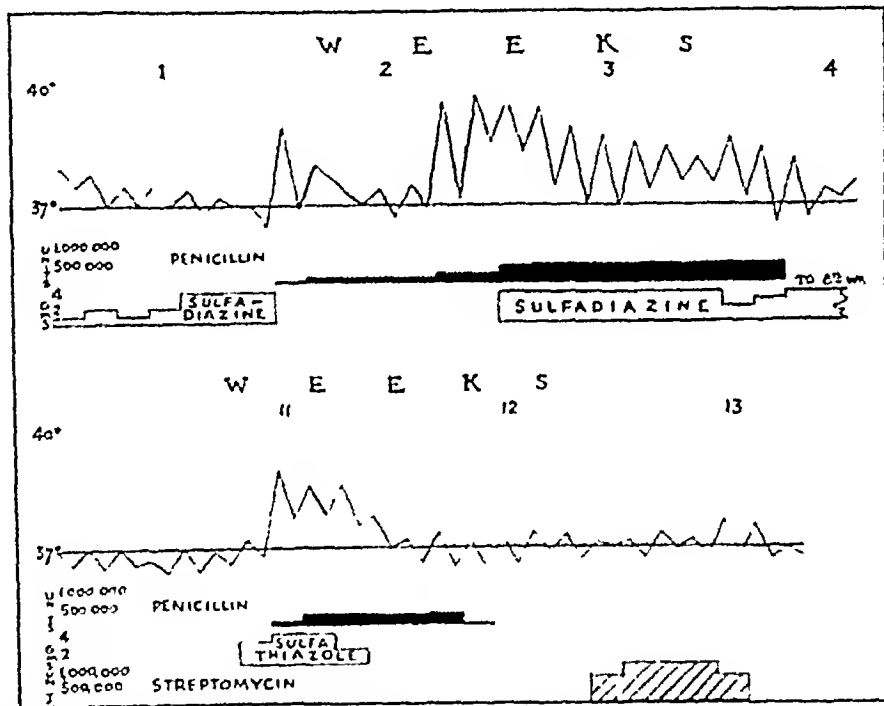


Fig 10—Postpartum pelvic and femoral thrombophlebitis, pulmonary embolism and urinary tract infection

stopped nine days after the pulmonary accident, sulfadiazine was continued since the urine failed to become free of organisms. The left leg remained swollen and changed very little.

After the infection appeared to be relatively quiescent, a cystoscopic examination was made on the seventieth day of hospitalization. A marked, shaggy cystitis was seen and a mild left pyelitis. Pyelograms revealed a bifid type of pelvis in the left kidney but no hydronephrosis.

Sulfathiazole was started on the day after the cystoscopic examination. This was ten days after sulfadiazine was discontinued and after the temperature had been normal for three weeks. The patient again had a chill and rise of temperature to 39°C (102.2°F) on the second day of sulfathiazole therapy. Penicillin was started immediately after the chill and sulfathiazole was discontinued on the fourth day because the fever was followed by conjunctivitis and urticaria. This suggested an

idiosyncrasy to sulfathiazole. The patient improved rapidly. Penicillin was continued for a week and then stopped. Urine cultures remained positive, the leg continued to be swollen and the temperature continued to be slightly elevated.

On the eighty-fourth day of hospitalization streptomycin was started.⁶ On the second day of this therapy the urine culture was positive. On the third and fifth days they proved to be negative for the first time since the first week of hospital treatment.

This case serves to demonstrate several points in the use of antibiotics and sulfonamide drugs. Apparently the infection became implanted during or at the termination of pregnancy. Pelvic thrombophlebitis was associated with urinary tract infection and eventually with involvement of the veins of the left thigh. The failure of response to sulfadiazine therapy may have been based either on an inherently resistant organism, an insufficient dosage or an infection too deeply seated within thrombosed vessels to be affected by circulating blood sulfadiazine. More than one of these factors may have been operating.

Although penicillin was not expected to affect the particular organism, it was instituted as a preventive measure when embolic signs became apparent because infarction of the lungs is likely to become complicated by respiratory organisms.

The bacilli did not disappear from the urinary tract until 1,000,000 units of streptomycin were given daily. This antibiotic was used only after it became apparent that the patient did not tolerate sulfathiazole, a commonly efficacious agent in urinary infections.

CASE V. A RESISTANT URINARY INFECTION WITH AN ENCAPSULATED COLIFORM ORGANISM (*AEROBACTER AEROGENES*) TREATED WITH ANTIBIOTICS INCLUDING STREPTOMYCIN

Miss A. P., aged 39, gave a history of having had an abdominal injury with a sharp-pointed instrument several years ago which resulted in the removal of an injured gallbladder. Later, she had performed a retrogasserian resection of the left middle branch of the trigeminal nerve for relief of the *doloreaux*. She also was operated upon on two occasions for hyperthyroidism.

She came to this hospital with a recurrence of hyperthyroidism. Her basal metabolism was considerably elevated and her neck was explored a third time. A piece of thyroid tissue was removed and her metabolism rate fell to normal. It was subsequently discovered that the patient had been taking large amounts of thyroid without advice from a physician. Her calcium and phosphorus levels were far below normal and it was necessary to administer parathyroid hormone and calcium to maintain a supratetanic level.

While recovering from the thyroidectomy the patient began to complain of mild low epigastric pain and severe left lower quadrant pain. No definite signs could be elicited. Later she had an attack of severe pain in the left lower quadrant associated with a bout of high fever. The abdominal wall in that area revealed marked splinting.

Leukocytes were present in a catheterized urine specimen but a culture was negative. The attack subsided. X rays of the gastrointestinal tract revealed a diverticulum in the second portion of the duodenum. The idea was entertained that she

might have a perforating diverticulum of the colon although it was not seen by x-ray following a barium enema

Some days later during her twenty-third week in the hospital, while under the influence of penicillin, an attack of left lower abdominal pain recurred and the abdominal wall was rigid. The temperature rose within four days to 40.5°C (104.9°F). The urine contained some leukocytes but the patient did not complain of urinary symptoms although it was known that she did have a urinary tract infection. The classical symptoms and signs of intra-abdominal infection made laparotomy imperative. A cystoscopy was done at the same time. The surgeon reported an enlarged left kidney but no other evidence of abdominal or pelvic disease. The left ureter was engaged by the cystoscope to the renal pelvis. A few leukocytes

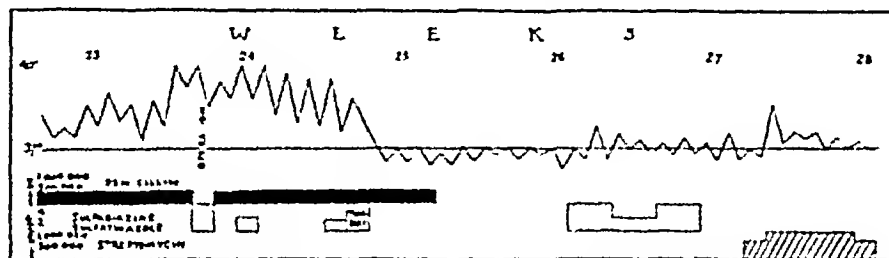


Fig. 11—Positive urinary cultures in pyelitis and cystitis that became negative only after streptomycin.

were obtained in otherwise clear urine. On culture from the left kidney mucoid colonies of encapsulated coliform bacilli were obtained. A blood culture was sterile. Sodium sulfadiazine was given on the day before and the day after operation. Penicillin was given pre- and postoperatively. The pyelogram made soon after operation showed no lesion of the renal pelvis.

An attempt to give sulfonamides for the cystitis and pyelitis was refused by the patient. Her temperature returned to normal on the seventh postoperative day but cultures of urine continued to be positive for the following three weeks. Although the patient insisted she could not tolerate sulfonamides, some sodium sulfadiazine was given parenterally with no apparent influence on the urinary infection. Streptomycin was started and urine cultures became negative on the second day of administration.

COMMENT AND SUMMARY

Experience is providing us with a wider and more detailed horizon in regard to the rational use of antibiotics. More and more we are learning their limitations as well as their values. We can better coordinate the qualitative variability of disease and the quantitative factor of dosage.

Of primary importance is the realization of the appearance of resistant strains of organisms that have been generally considered highly susceptible. That susceptible organisms can be "trained" to become resistant has been shown repeatedly in the laboratory but it is not so clear to what extent the natural occurrence of resistant strains has been fostered by routine therapeutic measures with antibiotics in the epidemiologic sense. At present it is probably wise to

consider such an effect as real and to make the attempt to avoid any encouragement of resistance

Two obvious paths are open in this respect. One is to allow the less serious infections that have usually tended to run self-limited courses to go untreated by antibiotics and so lessen the exposure of strains to resistance-producing agents. Such an approach is left to the good judgment of doctors and the teachings of those who have had adequate experience with infectious disease prior to the advent of antibiotics. Physicians trained recently would have to display considerable courage to allow disease to go untreated by antibiotics in spite of the widespread awareness by patients of the availability of such efficacious agents.

The second approach is based on the probability of rapid and complete eradication of all relatively susceptible bacteria in the individually treated patient. That may be attained through the use of large overpowering doses of antibiotics from the onset of treatment and their continued use for several days or weeks after the infection appears to have subsided.

Since penicillin is practically nontoxic except in specifically hypersensitive individuals, there seems to be no reason for the cautious approach in dosage except from the angle of expense. It appears at present that the dosage of penicillin should be from 400,000 units up to 2,000,000 units daily. The antibiotic should be administered for a considerable period after apparent complete recovery so that practically no susceptible organisms will remain to act as the nucleus of a resistant strain either to the same individual or to others by contagion. Reinfection with another strain or the same untreated strain would, theoretically, be susceptible to the same degree to antibiotics as the treated infection.

The use of larger doses of penicillin would also tend to overcome to a degree the variability in the activity of the several penicillins as prepared by the various pharmaceutical houses. This precaution must be kept in mind until the production of penicillin becomes uniformly standardized.

As a corollary to the above it would seem desirable to avoid treating an infection that is not obvious until the causative agent is clearly defined and the appropriate antibiotic is chosen. Then treatment should be carried out vigorously and thoroughly until the infection has either been thoroughly controlled or it has proved to be clearly resistant to the particular antibiotic. Half measures tend to confuse the diagnosis, the prognosis and the further treatment of cases and augment the resistance of bacterial agents to the antibiotics.

The above applies equally well to the elective use of antibiotics in prevention of complicating infections as applied in some of the cases described here.

The basic principles suggested here may apply to streptomycin but it is too early to evaluate that antibiotic in the same light

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ADVERSE REACTIONS TO THE SULFONAMIDES AND ANTIBIOTICS

MARY LOU EILERT, M D *

It is an unfortunate fact that there is available to the physician no effective antibacterial agent whose use is not occasionally attended by undesirable reactions. This has been particularly true of our most effective chemical antibiotics, the sulfonamides, and it is now apparent that the same is true of the biological antibiotics, particularly penicillin. Certainly every physician practicing today has had the misfortune to see in his daily practice adverse, sometimes fatal, reactions to the sulfonamides. Reports of reactions to penicillin are growing daily, although to the best of my knowledge there have been no fatal reactions reported to date.

The sulfonamides as a group have been responsible for a wide variety of reactions. Deleterious effects upon the blood and blood-forming organs include varying degrees of anemia, leukopenia and thrombocytopenia, as well as acute hemolytic anemia, agranulocytosis and acute purpura haemorrhagica.

Renal complications have been of two types¹ (1) an obstructive nephropathy due to precipitation of the drug, chiefly its acetylated form, within the renal tubules, and (2) an interstitial nephritis due to a direct toxic effect upon the tubular epithelium.

Toxic hepatitis, neuritis, arthralgia and psychoses have been reported with moderate frequency, while drug fever, skin rashes, conjunctivitis, mental depression, headaches, nausea and vomiting are reactions familiar to all.

Pathological material and experimental work² have demonstrated that an interstitial myocarditis characterized by infiltrates rich in eosinophils may be caused by sulfonamides. These drugs, either alone or in combination with antisera have been implicated in the etiology of some cases of periarthritis nodosa.^{3, 4, 5} Findings in our own pathology department have been in agreement, in regard both to myocarditis and lesions suggestive of periarthritis nodosa.

The mechanism of the reaction in each case is not always clear. Some reactions are the result of direct toxicity and are definitely related to dosage and blood level, others appear to be due to hypersensitivity of the individual to usual doses, such hypersensitivity probably being of the acquired or allergic type. A third suggestion has been that some toxic reactions are caused by liberation of toxins.

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from a chronic infectious focus due to the therapeutic effect of the drug. This, however, is difficult to prove.

The most severe and unpredictable reactions are probably due to an acquired hypersensitivity since these drugs are all powerful sensitizing agents. Sulfathiazole has been the greatest offender in causing sensitization, and a higher incidence of sensitization has followed local than oral or parenteral administration. Hypersensitivity, once acquired, may be to the whole group of drugs, to several but not all of the group, or to one drug only. Desensitization is apparently possible and is recommended by certain workers ^{6, 7}

Penicillin has a very low degree of direct toxicity and has therefore replaced the sulfonamides in the treatment of many common infections wherever it is available. Because of its method of preparation it was originally thought that any reactions occurring during its use were due to impurities. With the advent of relatively pure preparations it has become evident that some reactions are due to the penicillin itself, which, like the sulfonamides, is a rather potent sensitizing agent.

Reactions probably due to the penicillin itself include fever, urticaria, toxic and contact dermatitides, mild gastrointestinal symptoms and thrombophlebitis at the site of continuous intravenous infusions ⁸. Reactions regarded as being due to impurities have included chills and fever during the course of an intravenous or intramuscular infusion, headache, faintness, flushing of the face, burning pain at the site of intramuscular injection, tingling in the testes, muscle cramps, femoral phlebothrombosis, eosinophilia up to 30 per cent and an unpleasant taste after parenteral injection. Such reactions were more evident during the developmental period of penicillin therapy and were related to certain batches of the drug ⁹.

Clinical experience with streptomycin to date has been too limited to make possible any dependable statement regarding toxic reactions. Tender, indurated masses may persist for several hours at the site of injection ¹⁰. Fever, probably due to streptomycin, has also been reported. In one case of chronic brucellosis treated with streptomycin in this clinic a low grade fever persisted throughout the course of streptomycin therapy and fell promptly to normal after cessation of the drug. Subsequent events did not make it clear whether the fever was actually due to the drug or to the underlying infection, however.

CASE REPORTS

The following cases of adverse reactions to various antibiotics have been selected from those seen in this clinic during the past several years. They have been chosen with an eye to their interest and adaptability to discussion, and not necessarily because they illustrate a frequent type of reaction to the agent concerned.

Case I. Acute Hemolytic Anemia Due to Sulfanilamide

A 14 months old white male infant was admitted on the pediatric service March 7, 1940, acutely ill. During the winter he had had frequent upper respiratory infections, some of which had been treated with sulfanilamide.

Four days before admission he had developed an upper respiratory infection for which he was given 32.5 grains of sulfanilamide over a three-day period. The day before admission he had vomited several times. The morning of admission his skin and eyeballs were noted to be yellow, he vomited several times and passed a large quantity of what was described as bloody urine.

His temperature on admission was 100.5° F and there was a slight icteric tint to the skin. No abdominal organs were palpable. Hemoglobin was 8.5 gm. per 100 cc., erythrocytes 3,810,000 per cu mm and leukocytes 6950 per cu mm. with a normal differential save for 8 per cent young granulocytes. The urine contained 4 plus albumin and many red blood cells and casts. A nose and throat culture was positive for beta hemolytic streptococci and Friedländer's bacillus. The blood sulfanilamide level was 2.3 mg per 100 cc. On March 8 the Wassermann reaction was 4 plus and the Kahn negative, but on March 15 both the Wassermann and Kahn reactions were negative.

Treatment consisted of administration of 0.9 gm of sodium bicarbonate by mouth every six hours, four 100-cc. whole blood transfusions and sufficient parenteral fluids to maintain a good urinary output. No albumin was found in the urine after March 10 and no erythrocytes after March 13. The patient's hemoglobin on March 16 was 13 gm per 100 cc. and erythrocytes 5,270,000 per cu mm.

The patient was discharged March 22, but was brought regularly to the outpatient department. In November his mother reported a possible recurrence of hemoglobinuria following a cold, but urine examination in the clinic, including benzidine test and microscopic examination of the centrifuged sediment, was completely negative.

Comment—Sulfanilamide has been the chief offender in causing acute hemolytic reactions, and it seems probable that it was responsible in this case. The "bloody" urine passed at home doubtless contained large quantities of free hemoglobin, although by the time a specimen was examined here manifestations of acute damage to the kidney in the form of albumin, red cells and casts were the prominent features.

The absence of a palpable spleen, the normal leukocyte count and the absence of nucleated erythrocytes in the peripheral blood make it unlikely that the child had a primary acute hemolytic anemia which happened to coincide with administration of sulfanilamide. The rapid recovery after withdrawal of the drug and vigorous symptomatic treatment speaks against an acute nephritis or a hemolytic reaction due to invasion of the blood stream by the hemolytic streptococcus.

The most probable mechanism of the reaction is that it was on the basis of a sensitization to the drug. This is supported by the fact that the dose employed was not excessive, the blood level at the time of admission was low, and there was a history of previous administration of sulfanilamide.

The treatment in this case indicates a satisfactory regimen for treatment of acute hemolytic anemias due to sulfonamides, namely—

(1) immediate withdrawal of the drug, (2) alkalization of the urine to keep precipitation of hemoglobin within the kidney tubules at a minimum, (3) administration of adequate fluid to maintain a good urinary output, and (4) correction of the anemia by blood transfusions. It should perhaps be mentioned that after a reaction of this kind, subsequent administration of any sulfonamide should be undertaken with extreme caution.

Case II. Leukopenia Due to Sulfathiazole

A 48 year old white man hospitalized on the orthopedic service for treatment of a fractured leg and fractured ribs developed pain in the chest, rusty sputum, fever of 100.6° F. and x-ray evidence of a small area of pneumonic infiltration in the left lower lobe on November 15, 1941. Types XXIII and XXVIII pneumococci were isolated from the sputum, and the total leukocyte count was 8400 per cu mm. He received 7 gm of sulfathiazole orally on November 15 and 2 gm daily on November 16 and 17. A leukocyte count on November 16 was 7700, but on November 17 it had fallen to 2500. Sulfathiazole was immediately discontinued and the total leukocytes rose slowly to 5300 by November 22. His temperature fluctuated between normal and 101.0° F. during sulfathiazole administration. On November 19 it reached a peak of 101.8° F., then fell sharply to normal and remained essentially normal thereafter. A complete study of his blood by the hematology service on November 25 revealed a total leukocyte count of 5000 with 50 per cent neutrophils, 9 per cent eosinophils, 36 per cent lymphocytes, 1 per cent monocytes and 1 per cent basophils. Hemoglobin was 14.5 gm per 100 cc, erythrocytes 4,470,000 per cu mm, reticulocytes 0.9 per cent, erythrocytes appeared normal, and there was nothing suggestive of an underlying blood dyscrasia.

Comment—It is probable that an actual agranulocytosis would have developed in this case if sulfathiazole had been continued. The lack of any other evidence of hypersensitivity would have made it impossible to detect this patient's unusual sensitivity if daily leukocyte counts had not been done. Although there was no history of previous sulfonamide administration, the rapidity of onset and the 9 per cent eosinophilia suggest that he had previously acquired a hypersensitivity to the drug. The recent widespread use of various sulfonamides, particularly sulfathiazole, both orally and locally in the form of ointments, makes it unwise to assume that any administration of sulfonamides is a "first" administration. The view that hypersensitization is responsible for sulfonamide neutropenia is supported by Park.¹¹

Case III. Interstitial Nephritis and Acute Focal Myocarditis Associated with Intravenous Sodium Sulfadiazine Administration

A 57 year old white housewife, a known diabetic, was admitted to the hospital on January 28, 1943, acutely ill. On the day before admission she had had a chill, and had developed right lower chest pain. Admission findings were not diagnostic, but it soon became apparent that she had a pneumonia of the right upper lobe, and a Type V pneumococcus was isolated from the sputum. She had

TABLE 1--INTRAVENOUS SODIUM AND WATER FOR AL. ACCUMULATED FROM
INTRAVENOUS SULFADIAZINE IN CASE III

Date	Sodium Sulfadiazine	Dose sulfadiazine in blood (mg per 100 cc)	21 hr Urine Vol	Urine Findings	Blood NPN (mg per 100 cc)
1/20/40	5 gm 10:30 AM	190	100 cc	No WBC and casts	110
1/29/40	1 gm - 6:00 PM	71	1200 cc	low WBC and casts	
1/31/40	2 gm 1:30 PM	52	1175 cc	low WBC, low HBC, and casts	760
2/1/40		76	65 cc	Many HBC, low casts, no crystals	920
2/2/40		72	100 cc	Many granular and cellular casts, many HBC and WBC, no crystals	
2/15/40			19 cc		

had an episode of pyelitis in 1940 treated with sulfanilamide. Other points in her past history are not pertinent.

The treatment of the pneumonia consisted of specific antiserum and intravenous sodium sulfadiazine. Pertinent data are recorded in Table 1.

As may be seen, oliguria and increasing uremia developed beginning February 1. Few or no drug crystals were seen in the urine and bilateral ureteral catheterization on February 3 failed to reveal a block. The patient's diabetes was well controlled throughout, but the pneumonic process continued to spread in spite of sulfadiazine.

With the onset of oliguria her blood pressure, previously high, fell sharply, and she was digitalized with digalen. Nevertheless, pulmonary edema developed terminally, and she died eight days after the chill, five days after the first injection of sodium sulfadiazine and three days after the onset of oliguria.

Pertinent findings at autopsy, other than an extensive pneumonia, were in the kidneys and heart. Besides a mild chronic pyelonephritis and moderate arteriosclerosis the kidneys showed edema, tubular degeneration, granular and hyaline casts and an acute interstitial nephritis of the Councilman type. The exudate was strikingly condensed in streaks located near the corticomedullary junction. The cells were mainly mononuclear, some of myeloid cell type, but there were also a few mature neutrophils and eosinophils. Glomeruli were not entirely normal but showed only minor changes. There were no sulfadiazine crystals or concretions.

The heart showed a focal acute myocarditis with infiltrations of mononuclears, neutrophils and some fibrin. The pathologist suggested that the process in the myocardium was similar to that seen in other cases where sulfonamide sensitivity had been suspected.

Comment—The anuria in this case was apparently due to a combination of myocardial failure and extensive acute interstitial nephritis. The histologic findings suggested that both the myocarditis and the nephritis were caused by sulfonamides, probably on the basis of hypersensitivity. The relatively low blood levels and the history of previous sulfonamide administration lend support to this idea. The day before anuria developed 1345 cc of urine had been produced. However, 900 cc of this was obtained by catheter after a rather prolonged period of inability to void, and it is possible that this retention, possibly accompanied by a hypersensitivity, was responsible for irreparable kidney damage.

Sulfadiazine administration was stopped as soon as anuria developed and every effort was made to promote urine formation with no effect. The best and only treatment for such a reaction is prevention. At the present time penicillin would be the drug of choice for such a patient, and the above sequence of events would be avoided. The permission of a 900 cc. retention of urine is certainly to be condemned, and more frequent abdominal examination of any patient receiving intravenous fluid and not voiding properly should be performed.

Case IV. Unusual Sensitivity to Sulfathiazole, Sulfadiazine and Sulfanilamide

This patient, a 37 year old white woman, had for years had recurrent antral sinusitis for which a bilateral antrotomy was performed in April, 1941, and sul-

fathiazole powder instilled. Subsequently sinus washings often yielded chunks of undissolved sulfathiazole. In November, 1941, she developed a cystitis for which she received sulfathiazole at home as follows: 2.5 gm. the first day, 2 gm. the second day and 0.5 gm. the third day. On the evening of the first day she developed symptoms of an upper respiratory infection with nasal obstruction, coryza and a sense of substernal pressure. Neosynephria nose drops did not relieve the obstruction she became increasingly nervous and depressed and was therefore admitted to the hospital on the morning of the third day, November 28.

On admission the patient exhibited photophobia, diffuse conjunctival injection and bilateral nasal obstruction, apparently due to mucoid discharge. She received one additional 0.5 gm. dose of sulfathiazole at noon of this day. It was then discontinued because the nose and throat service thought the appearance of the nasal passages suggested a vasomotor rhinitis rather than a purulent sinusitis. Her temperature rose to 103° F. at 8 00 P M., but the following day she felt much improved and had no fever. Daily irrigation of the nose with tyrothricin was begun November 29, and she received 3 gm. of effervescent triple bromides a day. She continued to improve, but on December 2 developed an itching of the skin of the legs followed by a transient episode of giant hives. Bromides were discontinued, but on the following day a second attack of hives occurred with a rise in leukocytes to 13,250 per cu. mm. and an eosinophilia of 13 per cent. The hives subsided with injection of adrenalin, and the patient was discharged free of symptoms the following day.

Sulfadiazine, 0.5 gm. four times daily was prescribed for a recurrence of cystitis in November 1945. After several doses she noted itching of the skin, nasal obstruction and a recurrence of hives, so the drug was stopped. The cystitis failed to respond to argyrol irrigations and oral ammonium mandelate, so she was given 12.3 gm. of sulfanilamide over a four day period. On the day after sulfanilamide was discontinued, she developed a generalized urticaria similar to her previous skin reaction. Subsequent study by the allergy department revealed that she was sensitive to a variety of pollens and foods and that she had had rather frequent attacks of urticaria in the past not associated with sulfonamide intake. She also had subsequent attacks of urticaria although no more sulfonamides were administered.

Comment—In this case we have an example of an extremely allergic individual who had also acquired a sensitivity to sulfonamides, presumably through local implantation of sulfathiazole in the sinuses. Upon subsequent administration of sulfonamides she responded with an allergic type of reaction of the sensitized tissues, i.e., the respiratory tract, as well as with an urticaria identical with previous and subsequent attacks which must have been precipitated by different allergens. It is possible that the urticaria was unrelated to sulfonamides, but the fact that it followed administration of three different sulfonamides on three occasions strongly suggests an etiological relationship. It should perhaps be said that the local implantation of sulfonamides in sinuses has fallen into disrepute and is no longer practiced in this clinic.

Case V Toxic Dermatitis from Penicillin

A 73 year old white woman was admitted to the hospital with an infected sebaceous cyst of the leg. Administration of 40 000 units of penicillin intramuscularly every three hours was begun on May 15 1946. The cyst was excised on

May 16 and penicillin continued. On the evening of May 23, the tenth day of penicillin administration, the patient complained of itching of the skin, and on the following day an erythematous, maculopapular rash appeared. This was particularly marked on the trunk, but also involved the extremities. It was intensely pruritic. No constitutional symptoms or elevation of temperature occurred.

The last dose of penicillin was given at 8 00 A M. on May 24. The rash began to improve immediately and had faded entirely by May 26. The patient had not received penicillin before.

Case VI. Exfoliative Dermatitis from Penicillin

A 56 year old white man, a known mild diabetic, was admitted to the hospital July 22, 1945, because of pain in the chest and a temperature of 101.5° F. A diagnosis of right lower lobe pneumonia with effusion due to Type XXIII pneumococcus was made, and administration of 40,000 units of penicillin intramuscularly every three hours was begun July 23.

The patient was afebrile by July 27, but thereafter his temperature ranged from 98.8° F. to 101.5° F. On July 27, the third day of penicillin therapy, he developed an erythematous, maculopapular rash on the back and chest. The rash continued to spread, becoming intensely pruritic, and by July 30 involved the entire body except the face, palms and soles. By July 31 his hands, feet, ankles and eyelids were swollen and erythematous, and the skin of the chest and abdomen was beginning to desquamate. The erythema and edema increased and a mild conjunctivitis was noted August 1. At this time the pneumonic process seemed to be well controlled, so penicillin was stopped. The following day his temperature was entirely normal and remained so thereafter. The edema and erythema of the face increased slightly until August 2, but then disappeared spectacularly. Desquamation of the skin of the entire body continued until August 15.

On August 14 2000 units of penicillin in 0.1 cc. of normal saline and a control of 0.1 cc. of normal saline were injected intradermally. Similar skin tests with the same materials were performed on three individuals who had never received penicillin. No one of the three controls exhibited any reaction. The site of penicillin injection on the patient exhibited erythema, then wheal formation with increasing erythema and then well defined pseudopodia. At the end of twelve hours there were many small vesicles present which eventually ruptured, and desquamation followed. At the site of the saline injection there was only a temporary small wheal which was rapidly absorbed.

Case VII. Fever, Urticaria and Migratory Polyarthritides Due to Penicillin

A 31 year old white man with long-standing valvular heart disease developed a sore throat and fever. He immediately took 2 gm. of sulfadiazine, followed by 1 gm. a day for four or five days. Such a regimen had always terminated sore throats within a few days. Since irregular fever and malaise persisted, he presented himself at the clinic on May 9, 1946, approximately ten days after the onset of his illness.

Physical examination was negative save for a temperature of 100.2° F. and the previously determined large heart, systolic and diastolic aortic and presystolic mitral murmurs. The leukocyte count was 11,250 per cu. mm., hemoglobin 14 gm. per 100 cc. and the erythrocyte sedimentation rate was 27 mm. in one hour.

The patient was immediately admitted to the hospital for penicillin therapy with the idea of preventing a subacute bacterial endocarditis, and received a total of 1,755,000 units of penicillin intramuscularly over a four day period. Blood culture and nose and throat cultures were taken prior to treatment.

His temperature fell promptly and was entirely normal after May 11. Nose and throat culture revealed nothing abnormal, and the blood culture was negative on May 10. However, by May 12 a tiny gram-variable streptococcus had grown slightly in the broth culture but not in any one of four pored plates. In view of his apparent complete recovery it was thought that he had had merely a severe upper respiratory infection and that the broth culture had been contaminated.

The patient remained afebrile and was discharged on May 16. He returned to the outpatient clinic May 21 and said that slight fever had recurred on May 19 and May 20. His morning temperature at this visit was 99° F., so a venous blood culture was taken and he was sent home to bed until results were known. There had been no change in heart murmurs and no embolic phenomena. By May 23 the broth blood culture showed a heavy growth of a streptococcus morphologically identical with the one previously isolated and thought to be a contaminant. He was called into the hospital and a third blood culture taken May 23 yielded the same organism. It was eventually subcultured on blood agar, where it grew slowly and produced neither greening nor hemolysis of the surrounding media.

A diagnosis of subacute bacterial endocarditis was made and administration of 125 000 units of sodium penicillin intramuscularly every three hours was begun May 24. This large dose was adopted both because of previous failures in this clinic with doses as large as 500 000 units daily and because it was thought that the previous treatment might have resulted in an increased resistance of the organism to penicillin.

The patient's temperature was entirely normal by May 26 and remained so until May 29, when it rose to 99.6° F. at 4 00 P.M. On the morning of this day (the seventh day of his second course of penicillin and the twenty-first day dating from his first contact with the drug) he developed an urticaria of his hands, legs and perianal region. An intradermal skin test with 0.1 cc. of the penicillin solution he was receiving was strongly positive.

In view of the seriousness of his underlying disease it was decided that penicillin should be continued in the same dose although the rash was changed. He was also given 50 mg. of benadryl three times daily. Nevertheless the urticaria continued to spread spectacularly eventually becoming generalized with pronounced edema of the face and forearms. Figure 12 shows the eruption on May 31, the third day after its appearance. Temperature elevation reached a maximum of 102.6° F. on May 30. A maximum leukocytosis of 18 200 with only 1 per cent eosinophilia occurred May 31. He was extremely uncomfortable and very sleepy from the benadryl but he did not appear alarmingly ill and had no pruritus after benadryl was started.

On June 1 the urticaria appeared improved and by June 3 the sixth day after its appearance, it had disappeared entirely and the patient's temperature was normal. Following subsidence of the rash he developed a migratory polyarthritis, which first involved both shoulder joints followed by several days of fleeting pains in the fingers, knees and hips. This had subsided by June 9 and benadryl was then discontinued. With the onset of the arthritis he began to run a low grade fever which overexceeded 99.6° F. and this continued until penicillin was finally discontinued on June 29. An electrocardiogram on June 6 showed no essential change from previous tracings and on June 7 the erythrocyte sedimentation rate was 30 mm. in one hour and the leukocyte count 10 800 per cu. mm.

Intradermal skin tests were repeated on June 11 with both brands of penicillin he had received. The original brand gave an immediate swelling of 2 to 3 cm. diameter with slight erythema but no pruritus. The second brand resulted in slight transitory erythema but no edema and no pruritus. Neither one was at all similar to the initial skin test, and they were not considered positive.

On June 20, while still receiving penicillin, the patient developed a complete peripheral seventh nerve paralysis. The neurology service believed that this was a typical Bell's palsy unrelated to the underlying disease, since it seemed improbable that an embolus could produce such a picture. A blood culture taken on the day the palsy developed was negative. He continued to receive one million units of penicillin a day until June 29, having received in all 30,625,000 units over a thirty-seven day period.



Fig 12 (Case VII) —Generalized urticaria due to penicillin

The patient's temperature was entirely normal during the week following cessation of penicillin, and he was discharged on July 6. He has been seen twice in the outpatient clinic since that date and was permitted to return to work on July 22. There has been no recurrence of rash, fever or arthritis, and blood cultures taken each week for three weeks after penicillin was discontinued have remained negative. His facial paralysis has improved slightly.

Comment on Cases V, VI and VII—These three cases of reaction to intramuscular injection of penicillin have been presented in the order of increasing severity. The relatively mild type of toxic eruption illustrated by Case V has been seen frequently in patients in this hospital receiving penicillin. When, as in this case, the underlying disease

process does not require continuation of therapy, the treatment is clear, namely, discontinuance of the penicillin. Cases VI and VII, however, illustrate a more complicated problem where the possible risk and discomfort of a reaction are preferable to the greater danger of withdrawing therapy.

If a reaction occurs in such a case, it is advisable to change the brand of penicillin, since it is not clear whether certain reactions are due solely to the penicillin itself or to impurities. The efficacy of benadryl, an antihistamine drug, in controlling reactions has not been fully investigated, although it apparently relieved the pruritus in Case VII.

The early appearance of the dermatitis in Case VI in a patient who presumably had never before received penicillin cast some doubt upon penicillin as the causative agent. The subsequent course and results of the skin test seem nevertheless to substantiate the belief that this man's exfoliative dermatitis was the result of a penicillin sensitivity. It represents an unusually severe dermal reaction and one not reported heretofore. At no time, however, did the patient appear as acutely ill as is usual with an exfoliative dermatitis due to arsenicals, for example, and penicillin was therefore continued until the underlying disease process was well controlled. During the course of treatment, this patient received three different brands of penicillin, but the dermatitis continued to progress until treatment was discontinued. This supports the idea that the reaction was one of sensitivity to the penicillin itself and not to impurities.

Urticarial reactions similar to the dermal manifestations of the reaction in Case VII have been reported to occur in from 41 per cent¹² to 57 per cent⁹ of cases treated with penicillin. The lesions usually develop during treatment, but have occurred as late as nine days after treatment has been stopped. Some reports⁹ have indicated that the duration of the reaction is independent of continuance or cessation of treatment, but there is not universal agreement on this point.

The association of fever and migratory polyarthritis with urticaria in Case VII makes the whole picture similar to serum sickness save for the absence of generalized lymphadenopathy. Several similar cases have been reported.^{13 14 15} The course of the reaction and the change in response to intradermal tests would seem to indicate that desensitization occurred with continuation of the drug. The development of a Bell's palsy during penicillin administration was probably coincidental, as there have been no other reports of such a complication.

SUMMARY AND CONCLUSIONS

Four cases of reactions to various sulfonamides and three cases of reactions to penicillin have been presented and discussed. It has not been the purpose of this report to discourage intelligent use of these

valuable antibacterial agents by placing undue emphasis upon undesirable reactions. An effort has been made, however, to stress the fact that the sulfonamides have been associated with severe and even fatal reactions, whereas reactions to penicillin reported so far have been annoying rather than life endangering. This would seem to indicate that penicillin, when available, should be the treatment of choice for infections caused by susceptible organisms. Wherever sulfonamide treatment is clearly indicated, administration of the drug should be accompanied by careful observation of the patient's skin, temperature, leukocyte count, urinary output and cardiovascular status. The use of either group of drugs unnecessarily, particularly in the form of local therapy, is to be discouraged because of their strong sensitizing potentialities.

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THE USE OF THE NEW ANTIHISTAMINIC SUBSTANCES IN THE TREATMENT OF ALLERGIC DISORDERS

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EVER since the inference by Dale and Laidlaw⁸ in 1910 that histamine might be the chemical factor mediating the phenomena occurring in anaphylactic shock, its role in animal and human hypersensitiveness has been the subject of innumerable studies. In anaphylaxis the evidence is in favor of the view that many of the symptoms result from the liberation of histamine through the interaction of the antigen and its corresponding antibody on or within the tissue cells. The normal presence of histamine in the various body cells, especially in all the barrier tissues, has been proved by Barger and Dale,³ Best, Dale, Dudley and Thorpe,⁴ and others.

Dragstedt and Gebauer-Fuelnegg⁹ demonstrated the appearance of a histamine-like substance in the blood of intact dogs in anaphylactic shock. Dragstedt¹⁰ later in an explanation of this substance calculated that the blood from a 10 kilogram dog might yield 0.75 mg of histamine which, although too minute for chemical isolation, was fully adequate to account for the vascular reaction in anaphylactic shock. He concluded that the vasodepressor substance was most probably histamine, because it was the only substance found in mammalian tissues that met the chemical and physiological properties of histamine in all respects. He further emphasized the fact that histamine release is an important factor, but it is not the only one operating in the anaphylactic reaction. Code¹¹ is likewise of the opinion that the acute symptoms of anaphylactic shock depend upon the release of histamine from the tissue cells which have been damaged by the interaction of the antigen and antibody.

Histamine has three major physiologic actions: (1) it causes contractions of smooth muscles, (2) it dilates capillaries and increases permeability and (3) it acts as a secretagogue on secretory glands. Allergic patients react to histamine in an identical manner as they do to antigens for which they have sensitivity when it is injected into the skin, namely, causing an immediate reaction of the urticarial type. Katz¹⁵ devised a technic to test for histamine liberation in allergic reactions in the skin, and Rose¹⁶ demonstrated elevated histamine levels in the blood with the formation of extensive wheals in patients with dermatographia; he concluded that the histamine metabolism was disturbed in people with allergic disorders, because

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the histamine was within normal range but fluctuated widely whereas it remained constant in normal people. He was of the opinion that the physiologic reactions of histamine could explain the various acute manifestations of allergy occurring in man.

FOURNEAU COMPOUNDS

With the accumulating evidence of the vital significance of histamine in anaphylaxis and allergic diseases there has been a search for drugs and methods which would prevent the histamine type reactions. The most recent has been with the Fourneau series of chemical compounds following the observations of Fourneau and Bovet¹¹ in 1933 that phenolic ethers counteracted histamine action in vitro and in vivo. One of these, numbered 929F, was most effective but was too toxic for use. Staub²⁷ studied another Fourneau compound, 1571F, which was again of a toxicity too great to be of use therapeutically. Halpern^{13, 14} investigated a series of related compounds 2325RP (dimethylaminoethylethylaniline), and 2339RP (dimethylaminoethylbenzylaniline). They were found to be more specific against histamine than acetylcholine and barium chloride. He believed that the drugs modified the reaction of the organs so as to prevent histamine from causing its usual effects rather than preventing histamine from being liberated or destroying it.

Clinically the French investigators found the new drug 2339RP (Antergan) favorably effective in allergic conditions as a palliative remedy. The daily dose was from 100 to 1500 mg. for adults, half that for children, given every two hours. The side-effects were nausea, headache, vertigo, burning of the stomach and rarely vomiting.

Parrot²⁵ found that oral administration of 200 to 400 mg. of antergan prevented wheal formation and erythema from a 1:100,000 dilution of histamine hydrochloride twenty minutes after ingestion.

Another drug, 2786RP (Neoantergan), has been reported by Bovet and associates,⁵ which is reputed to be more effective than antergan and less toxic.

BENADRYL

Experimental.—In this country the synthetic drug, β -dimethylaminoethyl benzhydryl ether hydrochloride, or benadryl, has been studied by Loew and Kaiser¹⁸. They found it effective in preventing fatal experimental asthma in guinea pigs exposed to atomized histamine which killed 80 to 100 per cent of the unprotected control animals. Papaverine was twice as effective as aminophylline. The Fourneau compounds 929F and 1571F were eight and sixteen times respectively, while benadryl was thirty-three times as effective as aminophylline. The drugs were injected intraperitoneally. When the histamine was given intravenously instead of inhaled, the benadryl

was about half as effective as before. In toxicity studies 1571F had an LD-50 (lethal effect) for guinea pigs twice that of aminophylline while that of benadryl was about three times greater. In further studies Loew and Kaiser¹⁸ showed that it was of marked efficacy in decreasing the severity of anaphylaxis, this is further indirect evidence that the chief symptoms of anaphylactic shock are caused by histamine or similar acting substances. Dragsted and associates¹⁹ believe the mode of action to be that of competitive antagonism, the benadryl combining with the receptive substance and thereby disturbing the histamine equilibrium preventing it from combining with the same site to produce the anaphylactic symptoms. In anaphylactic studies with dogs they found that the benadryl reduced the vasodepressor effect of histamine, but not completely; therefore in its use in anaphylaxis one should not expect absolute control.

Pharmacologically, benadryl has three significant actions. It alleviates the bronchial constriction of histamine or anaphylaxis, the vasodepressor effects of histamine and the spasm of the smooth muscles.

Clinical.—The first clinical use of benadryl was in the treatment of eighteen cases of urticaria by Curtis and Owens⁷ with complete relief in eleven cases, improvement in three, and no relief obtained in four cases. The side reactions of drowsiness, muscular aches, dizziness and weakness were noted in some of the cases.

McElin and Horton²³ administered benadryl to patients by oral intramuscular and intravenous routes and found a decrease in the cutaneous vasodilation, in nasal congestion from vasodilation of the mucous membranes due to histamine. Also flare and wheal responses in cases of hypersensitivity to cold was depressed. The response of gastric acids and volume of gastric secretion due to histamine administration may be decreased by benadryl. Horton is of the opinion that the problem of edema as provoked by histamine release is the "common denominator" of allergic diseases and "is recognized in the mucous membrane at certain seasons of the year as hay fever and at others as vasomotor rhinitis. In the skin, localized edema manifests itself clinically as urticaria and angioneurotic edema, in the labyrinth as Ménière's symptom complex." Hay fever, vasomotor rhinitis, Ménière's disease, urticaria, angioneurotic edema and drug allergy (barbiturates and penicillin) were successfully treated with benadryl. However, Williams³⁰ reported that patients with Ménière's disease obtained greater relief from a combination of niacin and potassium nitrate than with benadryl. Histaminic cephalgia and atypical face and head pain were only partially relieved by the drug and it was considered as not being successful in these. One of three asthmatics obtained relief with it. The side effects were usually sleepiness, dizziness, dry mouth and jitteriness when present. There were no abnormal

changes in erythrocyte, leukocyte or differential blood counts, hemoglobin level or in urinalyses, platelet counts, bleeding and clotting time and blood urea nitrogens remained normal

The dosage of benadryl given orally was 50 to 500 mg. a day for adults in two to four doses. Logan²⁰ suggested 2 mg per pound (0.5 kg) as usually being the effective dosage for children given in two to four doses

O'Leary and Farber²⁴ had similar experiences with benadryl in the treatment of urticaria, namely, consistently good response. The drug is palliative and not curative, relief being obtained only while it is in use

The efficacy of benadryl in treating bronchial asthma is not as great as that in urticaria and hay fever. Koelsche and associates¹⁶ found that eight out of twelve or 69 per cent received no benefit while fourteen out of nineteen or 74 per cent with hay fever and asthma noted benefit. Of these, five noticed benefit from hay fever but not in the associated asthma

Friedlaender and Fernberg¹² found that the drug inhibited the production of wheals in patients by prior application to the reaction sites with both histamine and ragweed in sensitive patients although oral doses exerted only slight inhibition. Fifty to 100 mg. taken orally a few hours before skin testing abolished dermatographism. In studies of the effect of oral administration of the drug on blood pressure, a slight drop was noted in most cases. Clinically they found that the effect of the drug was palliative with a recurrence of symptoms upon withdrawal. It was effective in most cases of urticaria, angioneurotic edema and in relief of pruritus accompanying skin conditions. It seemed to be ineffective in the treatment of cases of perennial vasomotor rhinitis and nonseasonal asthma. A standard dosage of 50 mg three times daily was used, if no desirable results were obtained, this was increased to 400 mg total with individual tolerance permitting. Untoward side effects were drowsiness, lassitude, vertigo and dryness of the mouth.

Eyerman³¹ treated fifty-two cases of pollinotic vasomotor rhinitis, forty-eight due to ragweed pollen, and found the drug ameliorated discomfort totally in thirty-five cases (67 per cent), partially in twelve cases (23 per cent), and failed in five cases (9 per cent). In those partially relieved it prevented sneezing but nasal blockage persisted in seven cases, in those in which nasal blockage and sneezing were partially prevented a chest oppression and/or wheezing developed. A purulent discharge was present in six of these cases. Untoward symptoms appeared in some cases but disappeared when the dosage was reduced. A tolerance to the drug developed in some patients however when the same dosage was maintained whereas others noticed that the larger dose could be tolerated after an initial period on a small

dosage The usual objectional reactions to benadryl were somnolence, dry nose, vertigo, nausea, weakness, nervousness, palpation, insomnia and abdominal cramping. In two patients with an idiosyncrasy to aspirin he found that benadryl increased the bronchiospasm so that adrenalin was required. He found that twelve of fourteen cases of chronic urticaria were completely relieved while the drug was of no benefit in the treatment of primary polyposis, vernal conjunctivitis, dysmenorrhea and migraine The drug was palliative in effect with a recurrence of symptoms when medication was stopped

In a clinical study of benadryl Waldbott²³ noted that seasonal and perennial asthmatics failed to obtain the relief that patients with hay fever or urticaria received. With seasonal bronchial asthma nine patients (30 per cent) had complete, five (16 per cent) had partial, but sixteen (54 per cent) had no benefit. In perennial bronchial asthma fifteen (32 per cent) experienced complete relief, nine (18 per cent) partial, while twenty-four (50 per cent) had no relief These figures are contrasted with 80 per cent of twenty cases of urticaria receiving complete relief, 51 per cent of thirty-one cases of hay fever with relief, while 23 per cent or seven had partial benefit. The action was palliative and the symptoms tended to return in four to six hours Somnolence, vertigo and muscular twitching were the objectional side reactions noted Three patients developed severe asthmatic attacks from it

In a similar study made by Levin¹⁷ on 223 patients with a variety of allergic symptoms, much the same conclusions were drawn. Those with urticaria and pruritus from allergic dermatoses obtained a more satisfactory relief than those with asthma Side reactions were noted and medication had to be discontinued in half of those where they were found In others the tendency was overcome by decreasing the dosage; a tolerance developed to the drug which permitted a return to the larger dosage with good therapeutic effects Palliative and temporary relief was obtained for three to six hours in duration Medication aggravated the symptoms in four asthmatic patients, in one with allergic rhinitis and in two with migraine

✓ PYRIDENZAMINE

Experimental—One of the newest histamine antagonists is N-pyridyl-N benzyl dimethyl ethylenediamine monohydrochloride (pyribenzamine), a compound related to 1571F Mayer, and others^{21 22} found that standard intravenous doses of the drug would protect guinea pigs against 100 lethal doses of intravenous histamine whereas the original 1571F compound protected against only four to six In inhalation experiments, oral doses as small as 0.1 mg. per kilogram of body weight of the drug protected the animals fully for two hours, with six hours protection being obtained with 1 mg. per kilogram of body weight One milligram of the drug per kilogram of body weight

intravenously prevented wheal formation with injections of histamine phosphate in albino rats. Here, too, the mechanism of the reaction is a competitive one with histamine for its usual site of action.

Clinical.—Arbesman and associates¹ found that this drug administered orally reduced the wheal formation in eighteen of twenty-eight patients to histamine, and also in fourteen of twenty-four allergic patients it diminished skin reactivity. In normal patients passively sensitized with serum containing cottonseed reagents, pyribenzamine reduced the size of the reaction. It required higher concentrations of the serum to produce a positive reaction following the pyribenzamine.

In a later clinical study of the drug Arbesman and his co-workers² found that the effective adult dosage was 100 to 400 mg daily, while that for children varied from 50 to 200 mg.

In a total of 106 patients with ragweed hay fever, 84 per cent benefited from pyribenzamine medication, twenty-three of thirty-four patients seen obtained definite relief, with rhinorrhea, sneezing and other symptoms all diminished. Symptoms recurred when medication ceased or placebos were substituted. Seven of ten patients who had received preseasonal treatment without relief obtained relief from the drug. Of this number, eight had bronchial asthma due to grasses, seven obtained relief from the nasal symptoms but only four had bronchial symptoms alleviated also. Of sixteen patients with asthma due to ragweed, seven had complete relief while twelve obtained relief from nasal symptoms only. They found that pyribenzamine coupled with ephedrine and/or aminophylline controlled nasal and bronchial symptoms better than any one used alone. Twenty-eight of sixty-two patients with extrinsic bronchial asthma noted improvement after medication with the drug, pyribenzamine was of greater use prophylactically than therapeutically in treating bronchial asthma. Forty-four of forty-seven patients with acute urticaria were benefited while eighty-four of 107 patients with chronic urticaria obtained relief. The usual side reactions were drowsiness, dizziness, headache, excitability, palpitation, nausea and dryness of the mouth.

In some cases the drug apparently had a prophylactic effect on offending allergens. In a physical allergy to cold the typical urticarial wheal failed to develop in patch tests with ice cubes when pyribenzamine was administered prior to the test. People sensitive to cat and dog dander when exposed to the animals experienced mild or no reactions at all fifteen to thirty minutes after taking 100 mg of pyribenzamine.

CLINICAL EXPERIENCE WITH BENADRYL AND PYRIBENZAMINE

In our clinic 147 patients received treatment with benadryl or pyribenzamine for the allergic disorders indicated in Table 1.

TABLE 1 —RESULTS OF TREATMENT WITH BENADRYL OR PYRIBENZAMINE

Diagnosis	Number of Patients	Relief		
		Complete	Partial	None
Urticaria	46	34 (74%)	5	7
Hay fever	38	24 (63%)	3	11
Vasomotor rhinitis	30	14 (47%)	5	11
Hay fever with seasonal asthma	20	8 (40%)	3	9
Intrinsic asthma	42	10 (32%)	5	27
Total	176	80 (51%)	21	65

The dosage used varied from 50 to 400 mg daily divided in four equal portions, and it was further adjusted to meet the variation of the allergic state of the individual and the degree of exposure to the offending allergen. During the peak of the hay fever season some patients required twice or three times the dose used in the first and latter part of the season.

The relief obtained in urticaria and hay fever was marked while that in intrinsic asthma was relatively poor. The decrease of relief in asthma was also observed in the cases of hay fever with seasonal asthma, wherein several patients had relief of the nasal symptoms without a change in their bronchial asthma.

In forty-four patients under hyposensitization treatment for hay fever but experiencing symptoms during the hay fever season, the drugs afforded relief in thirty-eight cases.

The side reactions of sleepiness or drowsiness were the chief complaints in 52 per cent of the patients using this type of treatment. In addition, dizziness, dryness of the mouth, nervousness, epigastric distress and some interference in coordination occurred in some of the cases. When the side reactions were severe or interfered with the patient's occupation even with reduced dosage, the drug was discontinued. A poor initial drug tolerance was frequently overcome by decreasing the dosage for a short period of time and then reverting to the higher dosage level.

In our hands the drugs were equally effective in treating allergic disorders, however, benadryl was prone to cause sleepiness more often than did pyribenzamine while the latter caused more epigastric distress and nausea.

CONCLUSIONS

From a clinical standpoint, the value of the antihistaminic drugs appears at present to be in the field of affording temporary symptomatic relief to certain of the allergic manifestations. Their significance in diagnosis and other aspects of the allergic state must await further studies. Meanwhile, they can only be considered as new drugs of certain value but with troublesome side reactions which often limit their use.

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THE TREATMENT OF PNEUMONIA

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With chemotherapy so readily available and so generally effective, pneumonia is now treated with far greater assurance of recovery than just a decade ago. Prompt administration of sulfonamides or penicillin at the onset of a respiratory infection may either prevent pneumonia, or if it is present, with or without recognizable findings, stop its further development and be the means of a prompt recovery. This result materially lessens the need for hospitalization or prolonged nursing care in the home, so important in the past. However, this general effectiveness may result in a less thorough study of the clinical condition and consequent lack of knowledge of the etiology and character of the pneumonia present. It may also lessen the assurance that the best form of therapy is being used, and confuse the accuracy of the prognosis. This is especially true if a patient is being treated at home where x-ray and laboratory studies are less easily utilized.

Acute pulmonary infections were more generally classified on an etiological basis when specific antipneumococcus rabbit serum was the most effective therapy available. Chemotherapy has been so effective that bacteriological examinations in pneumonia may be slighted even in hospital practice.

It is possible by clinical findings only to make a relatively accurate diagnosis of the character of pneumonic lesions and, bearing in mind the information obtained from bacteriologic studies of the past in similar clinical conditions, to select the most desirable agent to use in any given case.

LOBAR PNEUMONIA

Lobar pneumonia is commonly the most dramatic of pulmonary inflammatory processes. Although it may be preceded by an upper respiratory infection such as an acute cold, it can set in abruptly in a person otherwise in excellent health. A severe chill, fever, cough, sharp, sticking chest pain, increased respiratory rate and rusty or blood-streaked sputum are common symptoms. In early stages there may be little physical evidence of the pathological process present. There may be some physiological splinting of the affected side of the chest, a pleural friction rub, and temporary resonance of the involved lobe with diminished resonance from compression atelectasis of the

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adjacent lobe. As the imprisoned air is absorbed there is dullness of the affected lobe, with prolonged expiratory sound progressing to tubular breathing. This clinical picture may with reasonable accuracy be diagnosed as lobar pneumonia. If available, an x-ray film of the chest will show a dense, homogeneous shadow usually limited to a part or whole of but one of the lobes of the lung.

Bacteriologic studies have shown the pneumococcus to be the causative organism in as high as 97 per cent of the attacks of lobar pneumonia.

Sulfonamides—Two forms of chemotherapy are now available to combat pneumococcal infections, the sulfonamides and penicillin. Sulfadiazine is in general considered the sulfonamide of choice. Its ease of administration, general effectiveness and relatively low toxicity are the factors in its favor. Four grams may be given as the initial dose, or 2 gm. repeated two and four hours later. The subsequent dose is 1 gm. every four hours day and night until the temperature has been normal for forty-eight to seventy-two hours.

A characteristic result of such therapy is illustrated by the following case report.

E. W., a 40 year old man, was brought to the hospital on the fifth day of his illness. He had had a chill followed by pain in his left chest, fever, cough and yellowish sputum. His entering temperature was 104° F, his pulse rate 120 beats per minute and respiratory rate 32 per minute. There was dullness in the lower portion of the posterior of his left chest, with a friction rub in the left axillary space and increased breath and voice sounds in the left base. Type V pneumococci were found by the Neufeld slide method in his sputum. Four grams of sulfadiazine were given by mouth followed by 1 gm. every four hours. The patient's temperature dropped steadily in the succeeding thirty-six hours to 97.6° F and continued normal.

This dosage usually maintains a blood level of 8 to 12 mg. of sulfadiazine per 100 cc. of blood, an effective range.² A similar result may be obtained by giving a patient 5 gm. of sodium sulfadiazine in 100 cc. of distilled water intravenously, repeating this amount daily either as a single dose or in two doses of 2.5 gms. each in 50 cc. of distilled water at twelve hour intervals. This mode of administration may be used if the patient is in coma or having gastrointestinal symptoms which could interfere with oral administration.

Reactions due to sulfadiazine therapy may occur in at least 10 per cent of the patients to whom it is administered. There may be crystaluria with or without hematuria, but with deposition of the crystals in the kidneys a possibility. Renal complications may in a large measure be prevented by insisting on an intake of 3000 cc. of fluids daily. This will usually insure the passage of at least 1000 cc. of urine daily. Further insurance against hematuria may be obtained by prescribing 2 gm. of sodium bicarbonate three times daily to increase the solubility of the sulfadiazine.

Skin reactions, rashes or local areas of angioneurotic edema may develop. Unless sensitization has occurred as a result of previous sulfonamide therapy, these reactions may not begin until the therapeutic effect of the drug has been achieved. Even with the practical certainty of a rash developing because of its previous appearance when sulfadiazine had been taken by the patient, its severity and duration may be in part controlled by calcium therapy, calcium gluconate tablets orally, and Neo-Calglucon solution intravenously.

Fever appearing or increasing during sulfadiazine therapy may be due to the drug itself. If the drug is the cause there will be a steady decrease of the fever when it is withheld.

Blood changes such as agranulocytosis and anemia are uncommon and rarely severe. A leukopenia in the early course of lobar pneumonia, prior to treatment, is not necessarily an indication for withholding sulfadiazine. If it is possible to study the bone marrow by way of a sternal puncture, the smears are commonly found to show normal development of the granulocytes.

Penicillin.—Penicillin is now available for general use and sufficient experience with it has established the various means of administration, effective dosage and therapeutic value. Its cost is steadily declining. If toxic reactions occur with sulfadiazine therapy prior to the achievement of the therapeutic effect, penicillin may be immediately substituted. It is also desirable to switch to penicillin if there is an extension of the pulmonary lesion, if there is lack of improvement in the patient's general symptoms, fever or pulse rate, if oliguria occurs, or if infected pleural fluid or other foci of infection due to the pneumococcus develop.

Because of its lower toxicity penicillin is now the medication of choice in lobar pneumonia in patients having severe systemic disease, in the aged, those with congestive heart failure, when ascites is present from any cause, or if the patient is in shock or extremis. Penicillin is not only effective against the pneumococcus, but also against *Streptococcus haemolyticus*, the *staphylococcus*, and *Streptococcus viridans*. Hence it is the therapeutic agent of choice in lobar pneumonia when it is due to the latter organisms. Penicillin was first administered intravenously or intramuscularly, usually 20,000 units every three hours. Administration by either of these routes requires the patient to be hospitalized or have in attendance someone trained to give injections. There is now available a preparation of penicillin concentrating 200,000 to 300,000 units of penicillin in a mixture of beeswax and oil which can be given in a single daily injection. It is capable of maintaining an effective blood level for twenty-four hours.

Recent observations have shown that penicillin is effective when given orally. An example of such administration is the following.

T B., a man aged 48 had had a cough for two weeks, general aching for three days, pain in his right chest and some blood in his sputum. There was dullness in the lower half of his right chest posteriorly with tubular breathing and fine moist rales. X-ray study revealed a rather uniform density of the right chest. With a temperature of 103° F., pulse rate of 142 beats per minute and respiratory rate of 44 per minute, he was given 200,000 units of penicillin orally followed by 100,000 units every three hours. In six hours his temperature was 101° F. In twenty-four hours it was 98.4° F. with a pulse rate of 96 beats per minute and respiratory rate of 24 per minute. On the following day the penicillin was reduced to 50,000 units every three hours and so continued for two days. An uneventful recovery occurred.

Only about 20 per cent of penicillin given orally is effective in the blood stream. Buffered against the gastric juices, it should be given at least an hour before, and at least two hours after the taking of food. In more seriously ill patients the first six doses may be given at two-hour intervals. The initial dose should be 200,000 units, subsequent doses 100,000 units. Twelve hours after the temperature becomes normal the dose may be halved to 50,000 units every three hours for the next forty-eight hours. In staphylococcal infections it is well to continue the full dosage for two weeks after the temperature becomes normal.

Results of Chemotherapy—Prior to the use of specific therapy in lobar pneumonia, the average case-fatality rate at the Cook County Hospital, Chicago, over a period of twenty-five years, was 35 per cent, the lowest rate in any single year being 24 per cent, the highest 48 per cent. Analysis of the case records of patients with lobar pneumonia treated with chemotherapy in three male medical wards over a period of two years, revealed a case fatality of 12 per cent.¹ Forty per cent of those who died were practically moribund when they were brought to the hospital. Recovery was the rule with patients 40 years of age or younger regardless of the duration of their illness when they came under observation. There was a progressive increase in the case-fatality rate with each decade of life over 40 years. In addition, most of those who died had some chronic complicating condition, such as chronic alcoholism, cirrhosis of the liver, chronic nephritis or heart disease.

Adjunctive Treatment—It may be assumed that some of the patients who were in extremis when treatment was initiated, could have been saved had chemotherapy been instituted earlier. It is also true that lobar pneumonia in some patients afflicted with a serious chronic disease is merely the incidental reason for termination of life. There is then a third group of patients practically all over 40 years of age, many with a chronic disease which is compatible with longer living, who apparently do not respond to chemotherapy alone if it is not started within forty-eight hours of the onset of lobar pneumonia. It is through the recovery of a greater number of these patients that a further decrease in the case fatality rate in lobar pneumonia must

be sought To that end the valuable adjuncts of treatment should be instituted promptly. All the various means used in the treatment of lobar pneumonia prior to the advent of specific therapy are here applicable. Capable nursing care, oxygen therapy by tent or nasal catheter, cardiac medication in the event of known or developing myocardial weakness, blood transfusion with existing or developing anemia, sedation and hypnotics for nervousness and sleeplessness, are among the measures which may assist in the recovery of these critically ill patients

Antipneumococcus Serum.—In anticipation of the possible use of immune rabbit serum, the sputum of patients suspected of having pneumococcus lobar pneumonia, especially those over 40 years of age and having some chronic disease, should be typed and blood cultures made prior to starting chemotherapy. The results so obtained in the previously cited group of patients at the Cook County Hospital revealed that 30 per cent of those over 60 years of age had Type II pneumococcus infection, and two-fifths of these had a positive blood culture Twenty per cent had Type III organism in their sputum, all with a positive blood culture This meant that 50 per cent of the group had an infection with a strain of pneumococcus which usually has a case-fatality rate higher than many other strains

Immune rabbit serum is highly concentrated, permitting ease in administration, and has a minimum of reactions most of which are minor. When it alone is employed within the first ninety-six hours of the onset of a pneumococcic infection it is highly effective³ Used in conjunction with chemotherapy, it is even more effective within this period and may have a beneficial effect even after the fourth day of the disease Combining these two forms of specific therapy with the supportive measures indicated in each individual case in which the prognosis is dubious, offers a good assurance that everything possible is being done for the patient

ATYPICAL PNEUMONIA

Atypical pneumonia has received much attention in the past three years. There are apparently many clinical conditions included under this term⁴ It has included mild upper respiratory and fatal pneumonic processes. In general it is more frequent in adolescents and young adults. The patients tend to be ill for one to two weeks, then have a long convalescence. The most frequent symptoms are sore throat, headache, chills, fever, paroxysmal dry cough, subternal pain and generalized aching The pharynx is usually reddened. The lungs tend to be clear for several days with basal rales appearing about the end of one week Consolidation may never develop The leukocyte count tends to be normal If x-ray is available, there may be found only increased bronchial markings radiating from the hilum,

with possible irregular shadows interspaced, or there may be a more extensive mottling radiating from the hilum to the periphery, involving a whole lobe

There is no recognized single etiological agent though a virus origin has been given much consideration. Nor is there any specific treatment. Bed rest, general and symptomatic care are the rule. Diathermy has been used to relieve tightness in the chest and for the relief of the dry, hacking cough. X-ray therapy has in some cases apparently hastened the clearing of the chest.

There are some cases of pneumococcal pneumonia which in their symptoms, course and x-ray findings simulate atypical pneumonia⁶. Also in some cases of so-called atypical pneumonia streptococci are so numerous in the sputum that they might reasonably be assumed to be the causative organisms. For these reasons and also with the hope of avoiding complications due to the sulfadiazine- or penicillin-sensitive organisms, both sulfadiazine and penicillin therapy are used in full dosage in atypical pneumonia. The results are sometimes most gratifying.

BRONCHOPNEUMONIA

Bronchopneumonia may occasionally be a primary infection. As a rule it is secondary to other infections or disabilities. The organisms causing it are those inhaled from the pharynx or inspired air. Most frequently found are the pneumococcus, streptococcus, staphylococcus, *Micrococcus catarrhalis* and *Hemophilus influenzae*. The primary form simulates lobar pneumonia, but the pulmonary findings may be bilateral, the x-ray changes showing less homogeneity of the infiltration present. In the secondary form, there is usually a bronchitis with an onset of, or increase in fever, dyspnea, and rapid heart action. The physical findings are usually bilateral with patchy areas of consolidations developing and various types of rales present. X-ray may show irregular areas mottling about the lower bronchi.

Inasmuch as the organisms commonly causing the infection are usually sensitive to chemotherapy, sulfadiazine may be effective in some cases, but penicillin is more generally employed because of its wider range of usefulness. Dosage comparable to that used in lobar pneumonia is advisable. Expert nursing care and the various general measures used in lobar pneumonia should be employed since the bronchopneumonia is usually complicating an illness already present.

Special consideration should be given to those cases of bronchopneumonia occurring during or in the wake of such infections as acute sore throat, tonsillitis, influenza, measles and whooping cough. Frequently the organism known as *Streptococcus beta hemolyticus* is the etiologic agent. The severity of the infection and serious prognosis may require a blood level of sulfadiazine higher than in a pneumococcal infection. This may be obtained by the administration of 2 or

3 gm. of sulfadiazine intravenously daily in addition to the usual daily oral dosage. Because of the frequency with which empyema may occur in infections due to *Streptococcus haemolyticus*, the full daily dosage of sulfadiazine should be continued for a week after the temperature is normal.

If penicillin is employed as the therapeutic agent, 200,000 units daily has been found to be the minimum for optimal effect, given in divided doses at three-hour intervals, with 100,000 units daily continued for four days after the temperature becomes normal. In the event that empyema develops, penicillin may have to be continued for two to four weeks. Should sulfadiazine be the initial therapeutic agent and empyema develop, penicillin should be substituted just as in pneumococcal infections with localized exudates.

ASPIRATION PNEUMONIA

In aspiration pneumonia there is a necrotic as well as an infectious process present.⁴ This condition usually develops in patients with at least temporarily lessened cough reflex. It may occur in coma due to anesthesia, head injuries, cerebral vascular accidents or brain infections. It is also a possibility in acute dilatation of the stomach, bowel obstruction, paralytic ileus and in general cachexia from any cause. Regurgitation of the stomach contents may be followed by aspiration of some of the material into the lungs. Hyperemia, chemical irritation and necrotic changes develop in the bronchial mucous membrane, with possible desquamation of the bronchial tree and hemorrhagic and edematous changes in the lung. The organisms found are the same as in the stomach contents—gram-negative bacilli, gram-positive ameboid bacilli, diphtheroids and yeasts, in addition to the pneumococcus, streptococcus and staphylococcus. The onset of symptoms may be profound and lead to a diagnosis of shock, pulmonary embolism, coronary thrombosis, cardiovascular collapse or bronchopneumonia.

The diagnosis is based on the analysis of the whole clinical picture, the preceding clinical state, the mode of onset and the pulmonary findings.

The most important feature of treatment is the prophylaxis. Recognizing the possibility of aspiration pneumonia, the physician may prevent it by continual aspiration of the stomach in the favorable pre-pneumonic states and the use of parenteral rather than oral fluids until the patient's condition no longer requires these measures. The prognosis of aspiration pneumonia is grave and the death rate is high. It is true, of course, many patients would die soon from the predisposing condition. There is no specific therapy. Chemotherapy is used, especially penicillin, in the hope that the invasion by some of the aspirated organisms may thereby be controlled.

PNEUMONIA DUE TO FRIEDLÄNDER'S BACILLUS

Friedländer's bacillus may produce either a lobar or a bronchopneumonia. The bacteriological findings are required to make a definite diagnosis. Spontaneous recoveries do occur. Penicillin has not been effective in combating this infection. Sulfadiazine has been used successfully in some cases.² The organism is apparently sensitive to streptomycin and favorable results in this infection have been reported following its use.¹ Until streptomycin is generally available, general supportive and symptomatic care, together with what benefit may be received from sulfadiazine, is the best means of combating the infection.

SUMMARY

Prompt and adequate administration of sulfadiazine or penicillin in pulmonary infections that may be clinically diagnosed as probable lobar pneumonia usually results in rapid relief of symptoms and recovery of the patient. Advanced age, previously existent disease, and delay in the institution of adequate chemotherapy are largely responsible for the deaths that occur. A careful evaluation of the condition of patients with poor prognosis, together with bacteriological study of the sputum, blood cultures, administration of specific antipneumococcus rabbit serum in selected cases, and the utilization of the indicated supportive measures offer a possibility for recovery of more of these patients.

Although it is claimed that no specific treatment for atypical pneumonia exists, the possibility that the infection in some may be due to pneumococci or streptococci justifies the use of sulfadiazine or penicillin in full dosage in the course of the infection.

Bronchopneumonia, usually a complicating illness, may be due to either beta hemolytic streptococci or pneumococci. This pneumonic process should therefore be treated with sulfadiazine or penicillin in full dosage.

Aspiration pneumonia, a combined pathological process of necrosis and infection, should be guarded against and prevented if possible by stomach aspiration when indicated to lessen the possibility of pulmonary complications from the regurgitated gastric contents. Penicillin therapy in full dosage offers the best chance of combating the infectious element of this profound reaction.

Pulmonary infections due to Friedländer's bacillus may respond to sulfadiazine. Streptomycin therapy, when available, may be an additional therapeutic aid.

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THE ACUTE INFECTIOUS DISEASES

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GREAT changes have occurred within recent years in respect to nearly all the acute infectious diseases. Diminished prevalence, fewer serious complications and lower fatality rates have been observed in almost every section of this country. Something more than progress in methods of immunization and introduction of new forms of therapy has contributed to these improvements in the general state of the public health. Advancement in sanitary science has been a powerful force in the curbing of mortality. Moreover, better homes and a higher scale of living have undoubtedly led to an improved state of nutrition. As a consequence, it seems reasonable to assume that resistance to infection has increased even if pathogenic organisms have not lessened their virulence. But if there has been both an increase of resistance to infection in the general population and also a diminishment in the virulence of disease, then death rates should have declined, even without improved methods of treatment. This last situation seems to exist in respect to certain diseases, notably smallpox and scarlet fever.

DIPHTHERIA

Diphtheria may be linked with smallpox from the standpoint of prevention, which is the only certain means of eliminating mortality from these diseases. The most expert care will not save the lives of all diphtheria patients. Even in the largest cities, however, remarkable success in stamping out diphtheria is possible when a program of immunization is well planned and energetically directed. Chicago is a good illustration of such an accomplishment. Figures from the Municipal Contagious Disease Hospital serve as an index of diphtheria prevalence in that city. In the year 1921, there were 2165 diphtheria patients admitted, in contrast to only twenty-three admissions, with one fatality in 1945.

Chicago's record in respect to diphtheria is particularly cheering at this time when the disease is said to have an increased incidence throughout most of the war-torn world. Even in this country the United States Public Health Service reports that diphtheria has ~~been~~ 24 per cent during the first three months of 1939, as compared with the first quarter of 1947.

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Treatment.—For the treatment of diphtheria patients, the mere administration of diphtheria antitoxin is not always sufficient. *Absolute rest* is sometimes equally important because of the danger of myocardial weakness. In serious cases the patient should not even raise his head from the bed. When myocarditis develops it is not likely to be detected prior to the tenth day of disease, and the slightest exertion may then be disastrous. If the patient has been ill without antitoxin for three or more days, we give 10 per cent *glucose* in distilled water intravenously each twenty-four hours for at least eight days. The amounts usually vary from 500 cc to 1000 cc, depending on the size of the patient. We believe that if 60,000 units of *diphtheria antitoxin* will not bring about recovery in a patient, he will seldom get well on double that amount. It is best to inject the antitoxin in the outer muscles of the thigh. Since the adrenals are often damaged in severe types of diphtheria, *adrenal cortical extract* in doses of from 3 cc to 5 cc, once or twice daily seems to be helpful in some instances. It is also our impression that for severe cases *penicillin* is a valuable adjunct in treatment. This drug is given in doses of 10,000 to 20,000 units intramuscularly every three hours. As long as a diphtheria patient has a pronounced albuminuria, he should not be regarded as out of danger. The presence or absence of albuminuria is exceedingly dependable as a prognostic guide.

Carriers.—Penicillin appears to be of value in freeing the nose and throat of diphtheria organisms. For this purpose the drug may be used as a spray, given in the form of a lozenge or injected in the muscle. The removal of tonsils and adenoids is likely to be successful when other measures fail.

SCARLET FEVER

Scarlet fever provides some of the most difficult problems in the field of public health. Whether or not it is controllable depends somewhat upon our conception of the disease. If scarlet fever can occur without a rash, it is not likely to be recognized, and so the individual may convey the infection to others. A patient with a diagnosis of streptococic sore throat is likely to be admitted without question to any general hospital. However, if a rash is observed, the disease is called scarlet fever and the patient is excluded. Nevertheless, the inciting organism may be the same in both instances. A large percentage of an urban population often harbors hemolytic streptococci in the nose or throat. This situation in respect to hemolytic streptococcus carriers among the civilian population has been reflected in military centers and has sometimes resulted in many cases of scarlet fever. An increase in scarlet fever generally means an increase in rheumatic fever and, therefore, the former disease becomes of major importance. There is no known method of establishing active immunity against

streptococcic infections. Consequently, if we acknowledge that scarlet fever can occur without a rash we must also admit that there is no agent available for inducing active immunity against this form of scarlet fever. Scarlet fever is far less prevalent and much milder today than only a few years ago and, consequently, deaths are fewer.

Treatment.—Serious and even fatal complications have sometimes followed what appeared to be a mild attack of scarlet fever. Therefore, even though the patient may not seem to be very ill, it is often advisable to administer one of the following therapeutic agents: convalescent scarlet fever serum, scarlet fever antitoxin or penicillin. The sulfonamides are not included here in the list of remedies, because we believe they do not influence the toxemia of scarlet fever. Nor do the sulfonamides seem to serve as a prophylactic against complications, although they are of value in treating certain complications.

Convalescent scarlet fever serum in doses of 20 cc. or more is of value. Because of a number of known instances in which acute hepatitis followed the injection of pooled human serum, however, there are now some who oppose the use of human convalescent scarlet fever serum. Convalescent scarlet fever serum may be given intramuscularly or intravenously at any stage of the disease but preferably early. *Scarlet fever antitoxin* in doses of 9000 units consists of only about 5 cc. or less by volume. It is now so highly concentrated and refined that unpleasant reactions are rare. To be effective, it should be given before the rash has disappeared, which means, as a rule, before the third day of eruption. It should be injected in the muscle. It is not recommended for the treatment of complications.

Our experience during the last year and a half with the use of *penicillin* suggests that this new drug is a useful remedy for scarlet fever. The intramuscular injection required for its greatest effectiveness is, however, a disadvantage in administration. Treatment consists in the injection of the drug in 10,000 to 15,000 unit doses every three hours.

It is stated that penicillin, when given in adequate dosage, will eliminate hemolytic streptococci from nose and throat within seven days. When used orally or in the form of a spray, penicillin is not so effective for eradication of hemolytic streptococci.

Lately, penicillin in peanut oil has been made available. It is claimed that when this preparation is injected in 300,000 unit doses intramuscularly about every three days it is as effective as when smaller doses are injected every three hours. We have not yet had sufficient experience with the oil preparations to judge their usefulness. There are some who strenuously object to the use of penicillin in peanut oil on the grounds that sensitization is not infrequent and that asthmatic attacks are produced.

MEASLES

After the first six months of life susceptibility to measles is practically universal at any age for those who have not had the disease. Before six months measles is uncommon, and under four months the disease is rare. It may be assumed that one attack of measles confers a lifetime immunity.

There is no known method for establishing an artificial active immunity. Passive immunity may be accomplished in one of several ways: *Convalescent measles serum* in doses of 7.5 to 10 cc., *immune globulin* (placental extract) 2 cc. to 5 cc., or the newer preparation developed through the processing of blood by the Red Cross, *gamma globulin*, 2.5 cc. to 5 cc. To be effective for prevention, any one of these substances should be given by the intramuscular route within three days of exposure. If it is desired to modify an attack of measles, five to six days should be allowed to elapse after exposure before making the injection. For prevention, sometimes two doses of the material are given, the first dose as soon after exposure as possible and a second dose five to six days later. It must be remembered this is merely a temporary protection that may endure for only two or three weeks. If the patient has a modified or attenuated attack of measles, immunity is likely to be permanent, although this is sometimes questioned.

Treatment.—Measles is a respiratory disease, and this fact should be kept in mind. Good ventilation is a requirement for proper care and undoubtedly lessens the possibility of a complicating bronchopneumonia. The value of *amidopyrine*, to which we were probably the first to call attention many years ago, has not been altered in my opinion. This drug may be given in doses of 1 grain (0.065 gm.) per year of age up to 5 grains (0.33 gm.), which was our original maximum. It is administered from three to four times daily for a period of three to four days and is best prescribed in a vehicle because in tablet form it occasionally causes nausea. I have never seen any harm result from the use of this drug when given in the manner described. *Amidopyrine* reduces fever, lessens cough, and apparently diminishes complications. It is much more effective than *acetylsalicylic acid*. *Convalescent measles serum* even in large doses is of doubtful value, and the use of *gamma globulin* for treatment does not seem to be justified. For patients with bronchopneumonia nothing is superior to the oxygen tent. *Sulfadiazine*, *sulfathiazole* and *penicillin* are beneficial.

Measles Encephalitis.—It has been estimated that encephalitis develops in about one in one thousand cases of measles. This complication seems to be much more frequent than twenty years ago. Measles encephalitis when present generally occurs before the rash has disappeared, usually on the fourth or fifth day of the eruption. The patient's future is always in doubt. More than one third of our

patients have seemed to make a complete recovery, sometimes, as many as one third have died, and others were left with permanent mental defects

The spinal fluid findings are not of diagnostic or prognostic significance. The fluid has a normal appearance and the cell count may be normal or increased, sometimes to 200 or more cells, which are nearly all lymphocytes

Treatment—Treatment of measles encephalitis often includes the use of an oxygen tent. The administration of 10 per cent glucose intravenously by the drip method is of value. We have frequently given also 200 cc or more of measles convalescent serum intravenously. Whether this latter procedure actually has any specific value is doubtful. Plasma as a substitute for convalescent serum when given in equal volume is probably as helpful. Whole blood transfusions are undoubtedly beneficial in some cases. Feeding by gavage may be necessary. Bronchopneumonia may terminate the patient's existence and, therefore, one of the sulfonamides or penicillin or both are often prescribed with the hope of forestalling this final complication.

After the temperature has returned to normal we have given some of our patients benzedrine sulfate in 5 mg doses once or twice a day. A few patients seemed much more alert after this treatment.

WHOOPIING COUGH

In recent years pertussis has accounted for more deaths than nearly all the other common contagious diseases combined. It is particularly fatal during the first year of life.

There is now available a number of vaccines for the prevention of whooping cough. Sauer's vaccine is undoubtedly the most popular in the Midwest. It is administered subcutaneously in three doses of 1, 2, and 3 cc. each at monthly intervals. Since each cubic centimeter contains 15 billion killed organisms (*Hemophilus pertussis*), the entire immunizing dose is 90 billion organisms.

Generally, it is recommended that antipertussis inoculations should not be given before the second half year of life. Eight months is often the age selected for this purpose. The reason for not making these injections early is because of the lack of antigenic response during the first few months of the baby's existence. However, it requires about four months to build up immunity, and if immunization is not undertaken prior to eight months, protection cannot be secured before one year of age. Consequently, those in early infancy who are in greatest need of a safeguard from pertussis are denied this benefit.

In 1940, the Committee of the American Academy of Pediatrics for the State of Illinois recommended in a pamphlet distributed by the Illinois State Department of Health that whooping cough immunization be undertaken at three to four months of age. This advice was

given on the theory that even if complete protection was not secured, a modified attack might occur if whooping cough was acquired, thus reducing the fatality rate, which is highest for those under one year of age

By means of a series of injections of pertussis vaccine, the pregnant woman is sometimes treated for the purpose of transmitting immunity to the unborn child. Success has been claimed by resorting to this method

Pertussis vaccine may be administered alone or in combination with either diphtheria alum-precipitated toxoid or tetanus alum-precipitated toxoid or both. Human hyperimmune pertussis serum may be used for passive immunity. There is now available a highly concentrated human hyperimmune serum which is sold under the name of *Hyper-tussis*. This product appears to be of undoubted value. It is injected intramuscularly in doses of from 2.5 to 5 cc.

Treatment.—Good ventilation, expert nursing, and proper feeding are the prime requisites for the average case of whooping cough.

Regardless of age, it is better to give nourishment in small amounts on many occasions than to give large quantities of food at greater intervals. If a baby suffers a paroxysm after taking its bottle, the contents of the stomach are likely to be evacuated. Under such circumstances about fifteen minutes are allowed to elapse and another bottle containing the prescribed formula is provided. It is very necessary that proper nutrition shall be sustained.

Patients with cyanosis or convulsions should be placed in an oxygen tent and may benefit from blood transfusions or hyperimmune serum. Hyperimmune rabbit serum has been available for some time but the concentrated human hyperimmune serum is a newer product.

For infants under one year of age, concentrated human hyperimmune pertussis serum may be given intramuscularly in doses of 2.5 cc. and repeated if necessary. Patients of any age should have the services of an oxygen tent when bronchopneumonia is present. Carbon dioxide has also been used, but we now believe this is unnecessary. Sulfathiazole or sulfadiazine is of value, and on some occasions penicillin has seemed to be definitely worth while when there are mixed infections.

Although it has been reported that streptomycin is effective for the treatment of pertussis, the drug has not been sufficiently plentiful to permit many to pass on its merits.

In hospital practice in Chicago we rarely resort to sedatives and prefer not to do so. However, if sedation is deemed necessary, chloral hydrate 5 to 10 grains (0.33 to 0.65 gm.) may be given by rectum or sometimes $\frac{1}{2}$ to $\frac{3}{4}$ grains (0.032 to 0.05 gm.) of seconal in a similar manner. For patients in the home, luminal in doses of 1½ to 3 grains (0.1 to 0.2 gm.) may prove to be very satisfactory.

MENINGOCOCCIC MENINGITIS

Undoubtedly the greatest progress in the treatment of acute infectious diseases in recent years pertains to the meningitides. In the past, practically all forms of bacterial meningitis were usually 100 per cent fatal with the exception of the meningococcic variety. In the case of the latter, although there had been a specific antiserum in common use since 1907, the results were far from satisfactory. Gover and Jackson state that the case fatality rate of cerebrospinal meningitis was 55 per cent in 1930 for the country as a whole, and that it was 39 per cent in 1940.

Prior to 1940, the year sulfonamides came into general use, the accepted method of administering serum was by the intrathecal route. In addition, frequent drainage of cerebrospinal fluid to relieve intracranial pressure was regarded as imperative. For these two purposes, daily lumbar punctures were considered a necessity. In some eastern hospitals this procedure was carried out as often as every six hours during the first few days. Even when Schwenker first reported the use of sulfanilamide for meningococcic meningitis, he injected the drug intrathecally.

Soon after beginning our clinical trial of Ferrys newly developed meningococcus antitoxin at the Cook County Hospital in 1934, we discontinued all intrathecal treatment in favor of the intravenous route. We also abandoned the long existing theory that repeated withdrawals of spinal fluid were necessary to relieve intracranial pressure. Furthermore, it was found that patients made excellent recoveries without any spinal puncture. The clinical diagnosis was confirmed by either a positive blood culture for meningococci or by a positive smear from petechiae when the latter were present.

During the few years of exclusive intravenous therapy at the Cook County Contagious Disease Hospital and also at Municipal Contagious Disease Hospital, we sometimes had lower fatality rates for meningococcic meningitis than we have ever had since the introduction of the sulfonamides. Much of our success was attributed not merely to the fact that large doses of serum were administered intravenously but because no irritating substance was injected intrathecally. Therefore, it is my opinion that a share of the remarkable efficiency of sulfonamide therapy should be attributed to the omission of intrathecal serum.

Unfortunately with the coming of penicillin after intrathecal therapy had at last been reluctantly discarded by many, there has been a disposition to resort again to intraspinal treatment. Yet, even those who advocate the administration of penicillin intrathecally admit the disadvantage of the method and confess that adhesions, and other complications sometimes occur. We continue to think that intrathecal therapy is not only unnecessary for any kind of meningitis but that it may be actually harmful.

Treatment.—The management of meningococcal infections may be as follows.

If petechiae are present, scarify one of the lesions, make a smear, stain and examine for gram-negative diplococci. Regardless of whether organisms are found in smear or not, always obtain blood for culture. The patient may have meningococcemia without clinical evidence of meningitis. If smear or blood culture is positive, a spinal puncture is not necessary. If the patient has no petechiae, a lumbar puncture is essential for examination of spinal fluid and prompt laboratory diagnosis.

Any of the principal *sulfonamides* may bring about recovery. Sulfadiazine, sulfathiazole and sulfamerazine are the chief ones for consideration. For practical purposes it is not obligatory to determine dosage on the basis of patients' weight but rather on the severity of the disease. For children under five years our initial dose of the drug selected is usually from 2 to 3 gm., followed every four hours by from 0.5 to 1 gm. Most of our patients are given either sulfadiazine or sulfathiazole.

Inasmuch as we administer the initial dose intravenously, a 5 per cent solution of either sodium sulfadiazine or sodium sulfathiazole is used. Although distilled water is generally recommended for the solution, normal saline will serve the purpose equally well. A 5 per cent solution of the drug will amount to 100 cc. by volume if 5 gm. is to be administered. This quantity is given by the drip method beginning with 10 to 15 drops per minute and gradually increasing the rate to 30 drops per minute, allowing about one and one half hours for completing the procedure. If there is any reason why the remedy cannot be injected intravenously and oral administration is not feasible, the drug may be given in a 2.5 per cent solution subcutaneously. We do not favor the use of a stomach tube for introduction of the sulfonamides. With the drug an alkali such as sodium bicarbonate may be used in equal or double amounts, or one sixth molar sodium lactate may be given intravenously. However, it is probably of greater importance to have an adequate intake of fluids. For this latter purpose, 10 per cent glucose or Hartman's solution is appropriate. It is well for the patient to receive from 2000 to 3000 cc. of fluids each twenty-four hours. The amount will depend upon the patient's age.

At any convenient time within twelve hours after the initial dose, it is well to determine the blood level for the drug employed. For sulfadiazine, a level of from 10 to 12 mg. per 100 cc. of blood should be expected and this figure approximately maintained. Sometimes the first level will be much higher. Sulfathiazole levels are likely to be low, and it is partly for this reason that sulfathiazole is not generally accepted as an appropriate remedy for meningitis. Sulfathiazole is, in fact, thoroughly efficient, notwithstanding the low blood levels and

the spinal fluid levels that are seldom more than 50 per cent or at most 70 per cent of the blood level. Because of the excellent therapeutic results obtained with sulfathiazole, we are inclined to believe that too much importance is bestowed on blood levels as a guide to dosage. Irrespective of the sulfonamide selected or the blood level reported, our plan of dosage is the same when treating any form of bacterial meningitis. In most cases of meningococcic meningitis, all sulfonamide therapy may be discontinued at the end of eight or ten days, and frequently in a lesser time.



Fig 13—A 14 year old girl admitted in coma to Cook County Hospital. Diagnosis: meningococcemia and meningitis. Massive hemorrhages on arms and similar lesions of lesser size on thighs and buttocks. Also petechiae on face and body. Treated with sulfathiazole and cortate. Photograph about eleven days after onset of illness shows sloughing of skin.

It is well to give adrenal cortical extract to patients with extensive hemorrhages in the skin, regardless of whether or not it is thought the Waterhouse Friderichsen syndrome exists. Comparatively few meningitis patients require sedatives but if such medication becomes necessary a barbiturate, chloral hydrate or paraldehyde may be administered. It is not advisable to give morphine.

Notwithstanding that penicillin seems to be an unnecessary adjunct to the sulfonamide treatment of most cases of meningococcic meningitis, it is distinctly beneficial for certain complications. For endophthalmitis, penicillin may be given both intramuscularly and intravenously or by iontophoresis with remarkably good results.

Prophylaxis.—On the basis of reports from military sources during the war, there appears to be no question in regard to the efficiency of the sulfonamides for prophylactic purposes. Several different plans of dosage were adopted. One consisted of giving a single dose, usually sulfadiazane, of 5 gm or more. In other instances the drug was administered in 1 gm doses two or three times a day for a period of three days to a week.

Should a case of meningococcic infection develop in one member of a family, it would seem logical to prescribe a sulfonamide, probably 1 gm. three times a day for each contact for a period of three days would be sufficient. Nevertheless, the experience in our contagious disease hospitals regarding this matter is interesting. Within a three-year period, 1943 to 1945 inclusive, nearly 3000 student nurses and probably half as many medical students came in contact with meningococcic patients. No one in either of the two hospitals was given any prophylactic remedy, no one wore face masks, and no one contracted meningitis.

OTHER MENINGITIDES

For the most part, what has been said in respect to the therapy of meningococcic meningitis applies to other forms of bacterial meningitis. There are, however, some differences which will be alluded to briefly.

Influenzal meningitis, which occurs most frequently in those under five years of age and very rarely in adults, still has a high fatality rate. While it is possible to bring about recovery by means of a sulfonamide drug, no patient should be deprived of the specific serum when the latter is obtainable. Type B anti-influenzal rabbit serum developed by Alexander is supplied in 25 mg ampules. It is well to give at least 50 mg intravenously and to repeat this dose if there is not some favorable response within twenty-four hours. At the same time, sulfonamide treatment is resorted to and sulfadiazane is often preferred. As a rule, the sulfa treatment should be continued for at least three weeks because there is a strong tendency for the disease to relapse.

Eventually streptomycin will probably displace entirely anti-influenzal serum as a therapeutic agent for influenzal meningitis. Present recommendations call for both intrathecal and intramuscular administration of streptomycin. However, I believe that if large doses—100,000 units (0.1 gm)—are injected intramuscularly every three hours for a

period of five to eight days, intrathecal treatment is not required. We have found that one spinal tap for diagnosis is usually sufficient, but the sulfonamide treatment should be continued for approximately two weeks after completion of streptomycin therapy.

Pneumococcal meningitis, regardless of the organism's type, responds well to the sulfonamides. Specific type serum intravenously sometimes seems to be helpful. Penicillin intravenously and intramuscularly is of value. Penicillin intrathecally is likely to clear temporarily the spinal fluid of organisms. Although we have had so many relapses and fatal terminations when penicillin was given intrathecally that we no longer follow this method, we are aware that there have been many favorable reports regarding intrathecal penicillin therapy.

Penicillin is particularly efficient for the treatment of streptococcal and also for staphylococcal meningitis when used intravenously and intramuscularly. In addition, one of the sulfonamides should be given.

Tuberculous meningitis is the only one of the meningitides in which some satisfactory response to treatment cannot yet be expected.

Streptomycin thus far has not been proved to be efficient in the treatment of tuberculous meningitis. Moreover, this new drug has not yet been used extensively enough to decide the full scope of its value or limitations in other conditions.

CLINICAL FEATURES AND TREATMENT OF BACTERIAL MENINGITIS

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TABLE 1 shows the incidence of the various types of bacterial meningitis in a recently studied series at Cook County Contagious Disease Hospital. Since those data were compiled, in addition to the varieties

TABLE 1—MENINGITIS AT COOK COUNTY CONTAGIOUS HOSPITAL.
MORTALITY REGARDLESS OF TREATMENT

December 1, 1913 to March 1, 1915

	Total No of Cases	Mortality, per cent	Died within 24 Hours of Admission	Corrected Mortality, per cent
Meningococcus	297	61 20.5	21	14.2
Pneumococcus	26	21 80.8	12	64.3
Mycobacterium tuberculosis	12	12 100.0	0	100.0
Hemophilus influenzae	10	5 50.0	1	44.0
Streptococcus viridans	3	2 66.6	1	33.3
Staphylococcus	1	1 100.0		100.0
Unidentified	51	3 5.9	1	4.0
Total cases	400			

listed, one case each of hemolytic streptococcus, lymphocytic (virus) and Bacillus coli meningitis has been encountered

DIAGNOSIS

To select in each case the most effective remedies from an armamentarium containing a variety of sulfonamides, specific antisera and potent antibiotics is a difficult task. Obviously, a knowledge of the etiologic agent is of the utmost importance. In general, with a spinal fluid cell count of 1000 or more per cubic millimeter, bacterial meningitis may be assumed. When the cell count lies in the range of 10 to

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100, poliomyelitis, encephalitis, brain tumor and syphilitic meningitis are to be thought of. In the range 100 to 1000, in addition to the conditions just mentioned, tuberculous or lymphocytic (virus) meningitis must be considered. However, a cell count of less than 1000 by no means eliminates bacterial meningitis as a possibility. In our series of 297 cases of proven meningococcal meningitis, 11.6 per cent of the patients who died and 15 per cent of those who survived had original spinal fluid cell counts of less than 1000. The presence of large numbers of bacteria with a relatively low cell count is a highly unfavorable prognostic sign.

In meningitis, as in any disease, a careful history and painstaking physical examination are necessary. For example, given the classical signs of meningeal irritation—headache, delirium or coma, rigid neck, positive Brudzinski's sign—such added features as petechial hemorrhages of the skin in meningococcal infections or cranial nerve involvement accompanying a previous tuberculous infection in other parts of the body in tuberculous meningitis are almost pathognomonic.

If errors are to be avoided, however, a search for the causative microorganism by spinal fluid smear and culture and blood culture in all cases, and by animal inoculation and cultures of other foci of infection in certain of them, must be made.

The prognostic factors, other than etiology, which influence the outcome must also be evaluated. These include mode of onset, age of the patient, delay in treatment, presence or absence of bacteremia, presence or absence of associated pathologic changes in the patient's body, and the glucose level of the spinal fluid. Frequent blood counts, urinalyses and determinations of blood and spinal fluid levels of the various remedial agents must also be made.

MENINGOCOCCIC MENINGITIS AND MENINGOCOCCEMIA

Since, during the war years, there has been an unusually high incidence of epidemic meningitis, it is not surprising that meningococcal meningitis or meningococcemia was diagnosed in 74 per cent of our cases. The latter diagnosis was made when signs of meningeal irritation were absent or minimal and the patient was covered with petechial hemorrhages with or without a positive blood culture. Sometimes spinal punctures revealed a few leukocytes in the spinal fluid, but usually there were none. Twenty-two of the 297 cases were considered to be primary meningococcemia. The others were diagnosed as meningococcus meningitis.

Table 2 reveals that meningococci were found by one of the means mentioned above in the majority of the cases in which the disease was attributed to this organism. The point that often only one of the diagnostic methods mentioned revealed the invading organism deserves special emphasis. Unless stained smears of the spinal fluid

are examined and spinal fluid and blood cultures are made before therapy is begun, some cases which might have been recognized will be overlooked. Some workers advocate examining smears of blood taken from the petechiae for meningococci. In a few instances we have found the organism in this way, but not often enough for us to consider it an important routine procedure. In the remaining 167 per cent of our cases, the etiologic relationship was assumed because

TABLE 2.—DIAGNOSTIC FINDINGS IN 297 CASES OF MENINGOCOCCIC MENINGITIS

Diagnostic Findings	No. of Cases	Per Cent of Total
Petechiae of skin present	176	59.2
Petechiae of skin absent	111	37.4
No record of presence of petechiae	10	3.4
Meningococci in gram stain of spinal fluid	197	66.3
Meningococci in cultures of spinal fluid	163	55.0
Meningococci in cultures of blood (179 cases had blood cultures)	67	37.4 (of those cultured)
Petechiae present in the absence of any positive bacteriologic findings	48	16.7
Meningococci cultured at necropsy but not ante-mortem	6	2.0

Results of typing of meningococci—119 cases

Type I .	114 (95.8%)
Type II	2 (1.7%)
Type IIA	3 (2.5%)

of the association of petechial hemorrhages with the other typical physical signs, after leukemia, thrombocytopenia and the other causes of petechiae had been ruled out. It is likely that the majority of the fifty-one cases of bacterial meningitis listed as unidentified were also caused by meningococci, but in the absence of any of the criteria indicated above, this diagnosis seemed unwarranted.

The Waterhouse-Friderichsen syndrome of extreme shock associated with large hemorrhages in the adrenal glands, and usually elsewhere in the body, was diagnosed five times—all in children under 10 years of age. These children all died. In the three cases in which autopsy was performed the diagnosis was confirmed.

Usually the meningococcal infection of the blood and meninges appeared to follow mild infections of the upper part of the respiratory tract—probably with this organism. Since this series was compiled,

meningococci were cultured from an aural discharge in two cases of meningitis. Possibly the route of infection was through the middle ear in these instances, but this is unlikely.

Treatment—As in all diseases, treatment must be individualized. In the presence of shock, which is seen frequently in meningococcal infections, plasma or whole blood transfusions in doses suited to the size and age of the patients, i.e., 100 to 250 cc for infants, up to 500 cc. and occasionally 1000 cc. for adults, and repeated in six to eight hours if there is not adequate response, are of paramount importance. Aqueous adrenal cortical extract or desoxycorticosterone in oil may be of value also, but the effect is less certain. If the blood pressure is extremely low, neosynephrin in doses of 0.2 to 0.5 mg (0.2 to 0.5 cc. of 1 per cent aqueous solution) by hypodermic injection may be of value. This may be repeated at intervals of two hours. A daily fluid intake of 800 cc in small children, up to as much as 3000 cc. in adults, must be maintained by parenteral injection if the patient is unable to take the fluid by mouth. Most patients with meningococcal meningitis will be receiving large doses of sulfonamides, hence should have 1000 cc. of one sixth molar sodium lactate solution each twenty four hours as part of their fluid intake unless 16 to 22 gm of sodium bicarbonate can be given by mouth each twenty-four hours. The sodium salts of the various sulfonamides cannot be added to this alkaline solution as they are precipitated in it.

Oxygen should be administered to patients who are cyanotic. For those who are extremely restless or delirious a sedative in the form of paraldehyde by mouth (4 to 12 cc for adults) or phenobarbital sodium (0.1 to 0.2 gm for adults) or sodium amytal (0.25 gm for adults) intramuscularly or ether in oil by rectum (30 to 40 cc. of ether with 90 cc. of olive oil for adults) may be given. Although opiates are known to depress the respiratory center somewhat, they should be administered if the headache cannot be controlled by other measures.

Foci of infection, such as otitis media, cervical adenitis and acute sinusitis should be searched for and given proper local treatment in addition to whatever specific measures are used.

Unless there are contraindications such as renal disease or a history of previous sulfonamide intoxication, one of the sulfonamides is usually the drug of choice in meningococcal infections. Sulfamerazine has given the best results in our own experience, although it has little advantage over sulfadiazine. Its isomer Sulfathiazole while distinctly useful, has been less effective. Our present plan is to give an initial dose of 4 to 6 gm of sodium sulfamerazine intravenously followed by maintenance doses of 2 gm every eight hours intravenously, or of 1 to 1.5 gm every four hours by mouth if the patient can retain the drug. With such doses the maximum blood levels averaged 219

mg per 100 cc Spinal fluid determinations made the same day averaged 13.8 mg per 100 cc. If sulfadiazine is used, 6 gm of the sodium salt intravenously as an initial dose, followed by 2 gm every six hours intravenously, or 1 to 2 gm every four hours by mouth is recommended. In our patients receiving this dosage, the average blood level was 17.04 mg and spinal fluid level was 14.07 mg per 100 cc. Since sulfathiazole is cleared more rapidly through the kidneys than the other sulfonamides mentioned, even larger doses of 8 to 12 gm. initially, followed by maintenance doses of 2 gm every four hours, must be used. Again it must be emphasized that, to avoid renal complications, an adequate output of urine should be assured by a fluid intake of 3000 cc. or more each twenty-four hours for adults and the urine should be kept at a pH of 7.5 or more. A sodium bicarbonate intake of 3 gm. by mouth every four hours around the clock or 1000 cc. of one-sixth molar sodium lactate intravenously each twenty-four hours for adults will usually accomplish this.

Some reports of series of patients with meningococcal meningitis treated entirely with penicillin compare favorably in their results with sulfonamide-treated cases.^{1, 2} Aside from the fact that it is more expensive and that the therapeutic effects are less prompt, we consider it equally efficacious, although we have treated fewer cases with it alone than with sulfonamides alone, or in combination with it. As with sulfonamide therapy, there is wide variation in the susceptibility of individual strains to penicillin. Consequently, if there is no response to adequate intrathecal administration, sulfamerazine or sulfadiazine should be added at once to the therapeutic attack.

While there have been isolated reports^{1, 2} of attainment of a therapeutic level of penicillin in the spinal fluid with intramuscular therapy in large doses alone, practically all workers agree that penicillin must be given intrathecally at least once in twenty-four hours, along with parenteral injections, to be effective. When using doses of 200,000 to 300,000 units intramuscularly every twenty-four hours alone we were able to demonstrate no penicillin in the spinal fluid. Using the serial dilution test suggested by Heilman twenty-four hours after 10,000 units were injected intrathecally in a series of ten patients, we found the average titer to be 0.69 units per cubic centimeter. We now use for adults an intrathecal dose of 20,000 units dissolved in 5 cc of physiological solution of sodium chloride, and for small children 5000 to 10,000 units, each twenty-four hours, until the spinal fluid culture remains sterile at least twenty-four hours and the acute symptoms have subsided. At the same time the patient receives 25,000 to 40,000 units (for adults) every three hours by intramuscular injection. This is continued until the signs of meningeal irritation have subsided and the patient has been afebrile several days.

In the treatment of patients who are poor risks for the reasons men-

tioned earlier, combined therapy with full doses of sulfonamides plus daily intrathecal doses of penicillin offers the most hope

When specific antiserum is available, its addition to the above program will probably make a *slight* improvement in the mortality rate among the patients who are extremely poor risks. During the past three years, we have been unable to obtain antimeningococcus serum.

PNEUMOCOCCIC MENINGITIS

Clinically, pneumococcic meningitis has the same features as meningococcic meningitis and cannot be differentiated except by careful bacteriologic study. Often it can be suspected because of the events preceding the onset of meningeal symptoms. In general there are four groups of cases which can be identified by their mode of onset.

Occasionally it is a *primary* manifestation preceded only by a mild infection of the nose and throat with no other detectable antecedent disease except paranasal sinusitis. Such cases have the best prognosis, although more than half of the cases of pneumococcic meningitis still terminate fatally. In another group of cases meningitis follows purulent otitis media and in this group the outlook is less favorable, though better than in the third group which usually follows extensive, confluent pneumonia. In the fourth group, in which purulent meningitis is a part of the clinical picture of vegetative endocarditis due to pneumococci, the outlook is well nigh hopeless regardless of what therapy is used. We, at least, have had no recoveries when endocarditis has been present.

As stated before, the diagnosis of pneumococcic meningitis should not be made unless pneumococci are found by one of the methods mentioned in the paragraphs on meningococcal meningitis. The blood culture is especially useful. In our last reported series (twenty six cases) it was positive in every instance.³ In those instances in which typing was accomplished, a wide diversity of types, between I and XVIII, was found.

Treatment—Treatment of pneumococcic meningitis must be heroic and prolonged. There is a marked danger of relapse if vigorous therapy is not continued for at least a week after apparent recovery. Sometimes it is wise to continue for even a longer period. In our experience, sulfonamides, on the schedule outlined above, constitute the most effective measure, and often penicillin is used in addition. Because of the extremely poor prognosis, one should also make an effort to type the organism so that antiserum may also be used in those patients whose response to other measures is poor. If it is decided to use specific antipneumococcus rabbit serum, a dose of 100 000 units for very young children up to 500 000 units for adults should be administered intravenously over several hours after the usual tests for serum sensitivity. A similar dose should be repeated next day if

the response is unsatisfactory. This biologic therapy may be the single added measure which tips the balance in the patient's favor

The relative frequency of pneumococcal meningitis in persons who have had skull fractures in the recent or remote past is an interesting feature with which all who have had much experience with the disease are familiar. Also worth remembering is its notorious tendency to relapse

HEMOPHILUS INFLUENZAE MENINGITIS

Hemophilus influenzae meningitis is a disease of young children. Adults are rarely affected. Particularly in infants with signs of meningeal irritation it should always be thought of. It should also be remembered that infants sometimes exhibit little rigidity of the neck, even when extensive meningeal exudate is present. The extreme apathy alternating with irritability when the child is aroused, and a temperature usually somewhat lower than in meningococcal meningitis often suggest tuberculous meningitis or encephalitis. The cell count, averaging about 5000 in our experience, is practically the same as for the other types of bacterial meningitis. The diagnosis again must be made by laboratory methods, in this instance the finding of pleomorphic, gram-negative bacilli in direct smears or cultures of the spinal fluid or blood.

Treatment.—Since the prognosis is almost hopeless without prompt and vigorous therapy, all of several distinctly useful measures for this serious disease must be considered and used in the appropriate combinations.

Streptomycin has proved very effective. It is given usually in doses of 50,000 to 100,000 units (0.05 to 0.1 gm) intraspinally after removing slightly more spinal fluid than the amount in which the streptomycin is dissolved. At the same time intramuscular doses are begun and continued at intervals of three hours day and night. The average parenteral dose is 100,000 units (0.1 gm) per kilogram of body weight each twenty-four hours, making a total twenty-four hour dose of 1 to 2 gm for most small children. The intrathecal dose is kept up once daily until the spinal fluid cultures remain sterile.

More experience with streptomycin may demonstrate its efficacy when used alone but we have usually reinforced it with sulfadiazine or sulfamerazine, using the dosage and technic outlined under Meningococcal Meningitis.

In addition, Alexander's specific rabbit serum should be used if the response to the above measures is not prompt and adequate. Alexander¹ has advised doses of 50 to 100 mg as the first dose. Subsequent dosage is determined by the presence or absence of demonstrable antibody against type B *Hemophilus influenzae* in the patient's serum next day. The test is performed by mixing a loopful of a suspension of *Hemophilus influenzae* organisms with one or two drops of the

patient's serum on a glass slide and examining microscopically for capsule swelling. The glucose level of the spinal fluid is also of value the need for serum being considered urgent if the level is below 20 mg. Usually a maintenance dose of 25 to 75 mg daily is adequate in small children. It may be safely discontinued when tests reveal sufficient antibody in the blood serum and the spinal fluid glucose level has attained 30 mg per 100 cc.

In spite of all the above measures the outlook in Hemophilus influenzae meningitis is still grave in children under three years of age. Treatment with streptomycin or sulfadiazine or sulfamerazine should be continued until the patient has been symptom free for seven to ten days.

STREPTOCOCCIC MENINGITIS

Streptococcal meningitis occurs less commonly than the types just discussed. When caused by the beta hemolytic streptococcus, it usually is a sequel of acute otitis media with extension to the mastoid and development of lateral sinus thrombosis. More rarely it follows acute paranasal sinusitis without middle ear infection. Response to sulfonylamides or penicillin, or these two measures in combination, is usually prompt and satisfactory. The technique of treatment is the same as that outlined for meningococcal and pneumococcal meningitis.

In our experience Streptococcus viridans meningitis is seen more frequently and response to therapy is much less satisfactory. It, too, may follow otitis media or paranasal sinusitis, but more often is a complication of subacute bacterial endocarditis.

After meningitis is present, the clinical findings differ in no way from those of the other types of bacterial meningitis previously described, except that the symptoms and signs of the antecedent infection are also present.

Penicillin must be used in full doses both intrathecally (10,000 to 20,000 units each twenty-four hours) and parenterally up to one to two million units each twenty-four hours in the cases associated with endocarditis. In addition, sulfadiazine or sulfamerazine, in the doses previously outlined, should be used. Appropriate local measures to insure drainage from the ear and sinuses, and mastoidectomy if indicated, must never be neglected.

STAPHYLOCOCCIC MENINGITIS

Fortunately, staphylococcal meningitis is extremely rare. It may be a part of the picture of staphylococcal septicemia or develop by direct extension from osteomyelitis of one of the bones in contact with the cranial cavity—usually the frontal. Hemolytic Staphylococcus aureus causes the majority of the cases and when present offers the poorest prognosis. In addition to prompt drainage of the focus causing the

meningeal infection, both penicillin and sulfadiazine, sulfamerazine or sulfathiazole should be used in the manner outlined for *Streptococcus viridans* meningitis.

TUBERCULOUS MENINGITIS

Tuberculous meningitis should always be considered when, together with the usual signs of meningeal irritation, a spinal fluid cell count of 100 to 1000 (lymphocytes predominating) is encountered. The tendency for a fibrin web to form quickly in the spinal fluid, which appears clear or only very slightly turbid, is well known. Occasionally tubercle bacilli may be demonstrated in the spinal fluid by the Ziehl-Nielsen stain, but this is exceptional.

If it is remembered that characteristically the base of the brain is chiefly involved in the meningitis caused by tubercle bacilli, whereas the vertex is chiefly involved in the other types of meningitis, many diagnostic errors will be avoided. Cranial nerve involvements, particularly strabismus, are common in tuberculous meningitis and rare in the other types. There is very often a history of tuberculosis elsewhere in the body, especially in lungs, bones, joints, lymph glands or gastrointestinal tract. Tuberculous meningitis is usually a part of the picture of disseminated primary tuberculosis. The Mantoux test is nearly always positive. The temperature is often only slightly elevated at the start and the patient may not appear as acutely ill as in the other types. The course nevertheless is relentlessly downhill with progression of the fever, vomiting, emaciation and loss of consciousness, in spite of all the usual types of therapy. We have had no recoveries. A few reports of prolongation of the course by massive doses of streptomycin have appeared, but there are no reports of recoveries to my knowledge.

MENINGITIS OF UNDETERMINED ORIGIN

This diagnosis should be made only after all the diagnostic methods described earlier have been employed. However, a small percentage of cases (12 per cent in our experience) will inevitably fall in this group.

If the signs of meningeal irritation are extremely mild, and there are no paralyses or absence of abdominal or cremasteric reflexes, and the deep tendon reflexes are intact, together with a spinal fluid cell count in the hundreds, lymphocytes predominating, lymphocytic choroiditis may be established as a working diagnosis. It can be confirmed only by animal inoculation. This disease is usually self-limiting, but it is safer to give one of the sulfonamides in full doses until recovery appears assured.

In poliomyelitis there may be signs of meningeal irritation at the start, but this disease should not cause much confusion. Usually, early in the course, there is much pain in the affected extremities and ex-

treme irritability without loss of consciousness or delirium. The spinal fluid cell count may be from 20 to several hundred with slight predominance of polymorphonuclears, later shifting to lymphocytosis and there is no pedicle formation. Later the characteristic loss of deep tendon reflexes and development of flaccid paralyses make the diagnosis unquestionable.

In the majority of cases of meningitis of undetermined etiology however, the clinical picture is that described for bacterial meningitis above, and the cell count is in the thousands. The major portion of such cases probably are caused by the meningococcus. Treatment should be with sulfadiazine or sulfamerazine in full doses with the addition of penicillin intrathecally and parenterally if progress is unsatisfactory.

SUMMARY OF TREATMENT OF SUPPURATIVE MENINGITIS

1. Make an etiologic diagnosis if possible
 - a. Spinal fluid smear. Spinal fluid culture. Blood culture
 - b. Complete blood count.
 - c. Look for petechiae—meningococcic meningitis. (Meningococci often found in smears from petechial hemorrhages)
 - d. Look for otitis media. Important aetium of infection in streptococcic, pneumococcic and in staphylococcic meningitis
 - e. Look for symptoms and signs of active endocarditis. Important for diagnosis and prognosis in streptococcic and pneumococcic meningitis
 - f. Examine lungs carefully. Important in pneumococcic and tuberculous meningitis
2. For patients in shock
 - a. Plasma or whole blood intravenously
 - b. Adrenal cortical extract in full doses.
 - c. Oxygen if patient is cyanotic.
 - d. Neosynephrin hypodermically

General measures

 - a. Fluids to 3000 cc. daily by mouth or intravenously (adults)
 - b. Drainage of foci of infection such as otitis media or acute sinusitis
 - c. Sedative for patients who are extremely restless
 - Paraldehyde.
 - Ether in oil per rectum.
 - Phenobarbital sodium or sodium amytal subcutaneously
3. Give *penicillin* in:
 - Meningococcic, pneumococcic, *Streptococcus viridans*, *Streptococcus hemolyticus* and staphylococcic meningitis
 - 20 000 units dissolved in 5 cc. of physiological solution of sodium chloride intrathecally after withdrawing 10 to 15 cc. of spinal fluid. Repeat every 24 hours until spinal fluid remains sterile on culture
 - 25 000 to 40 000 units every three hours by continuous intravenous drip or intramuscularly until spinal fluid and blood remain sterile on culture. Doses up to 1,000 000 units daily if the patient has bacterial endocarditis.
4. Give *streptomycin* in *Hemophilus influenzae* meningitis
 - 50,000 units intrathecally every 24 hours
 - 1 000 000 to 4 000 000 units intravenously every 24 hours or intramuscularly in divided doses every three hours

5 *Sulfonamide therapy*

For *Hemophilus influenzae* meningitis

For meningococcie, pneumococcie, *Streptococcus viridans*, *Streptococcus hemolyticus* and *Staphylococcie* meningitis and meningitis of undetermined etiology

a. *Sulfadiazine* (adult dosage)

First dose—6 gm intravenously.

Maintenance dose—2 gm every 6–8 hours intravenously
1–2 gm every 4 hours by mouth

or

Sulfamerazine (adult dosage)

First dose—4–6 gm. intravenously

Maintenance dose—2 gm every 8 hours intravenously
1–2 gm every 6 hours by mouth

b. *Sodium bicarbonate* (adult dosage)

Three grams every 4 hours by mouth, or 1000 cc. of $\frac{1}{6}$ molar sodium lactate solution intramuscularly every 24 hours

6 *Biologic therapy*

a. For pneumococcie meningitis (adult dosage)

Type-specific antipneumococcus rabbit serum, 200,000 or 300,000 units intravenously during first 12 hours—after ocular and cutaneous tests for sensitivity.

Then 100,000 to 200,000 units each 24 hours until recovery begins.

b. For *Hemophilus influenzae* meningitis

Type B anti-influenzae rabbit serum, 50 to 100 mg intravenously, as first dose.

Then 25 to 75 mg every 24 hours until patient's serum gives capsule swelling reaction with H influenzae.

c. For meningococcie meningitis not responding to penicillin or sulfonamides—antimeningococcus serum intravenously or intrathecally

d. For hemolytic streptococcus meningitis Consider convalescent scarlet fever serum

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ENCEPHALITIS

HEINZ KOHUT, M D *

INTRODUCTION

It is not easy to organize, categorize and define the notions one has formed about the subject matter of encephalitis. Literally translated the term means "inflammation of the brain." In other words, it does not stand for a disease entity or even a group of diseases but rather signifies a specific histopathological and physiological reaction of the brain tissue towards a variety of injurious influences. Such a concept, however, embraces so great a number of clinically and etiologically widely different syndromes, with but one common denominator, that it has only theoretical significance. It is best, therefore, to disregard the bacterial infections, like brain abscess and purulent meningitis, the "specific" inflammations, i.e., syphilis and tuberculosis of the brain, also the degenerative disorders, like multiple sclerosis and Schilder's disease, and the encephalitides secondary to metal poisoning, e.g., lead encephalitis. We shall also neglect the specific cases of encephalitis after vaccination and after certain virus diseases like measles, varicella and variola, and the clinically separate entities of rabies and poliomyelitis. We are then left to discuss a group of inflammatory diseases of the brain that have these three things in common: (1) certain histopathological similarities (diffuse but selective ganglion cell destruction, lymphocytic infiltration), (2) proved or at least presumptive causation by a filterable virus and (3) with certain exceptions, a characteristic clinical course.

The interest in these diseases is not usually very great—and that for good reasons. A number of them are rare. Some, like the Russian encephalitis, the Japanese encephalitis and the West Nile fever, occur in far off parts of the world. Others, like the western and eastern equine encephalomyelitides and the St. Louis encephalitis, occur with relatively greater frequency, although mostly in epidemics which are restricted to circumscribed areas. Such cases, however, require for their identification either the isolation of the virus or the proof that the patient has developed specific neutralizing antibodies in the course of the diseases—both procedures that fall into the domain of the immunologist or public health officer. Even the once so frequent epidemic encephalitis, which often runs a typical and recognizable clinical

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course, does not seem to occur any more in its characteristic form, although its continued presence can be surmised from the frequency with which its sequelae are still encountered. Last, but not least, the lack of interest in this group of diseases stems from the fact that, apart from mostly unsatisfactory attempts of active (prophylactic) or passive immunization and general supportive measures, no treatment which is worth the name has been found up to the present time.

A detailed description of the various disease entities, the qualities of their etiological agents, and the immunological reactions, in the present state of our knowledge does not therefore seem of great value. What is needed, however, is (1) the differential diagnosis of acute encephalitis as a group from other disease entities, some of which lend themselves to more promising therapeutic attempts or at least warrant a different prognosis, and (2) a discussion of some of the chronic sequelae which, as stated above, seem to present themselves more frequently in recent years than the acute disease itself.

SYMPTOMATOLOGY AND DIAGNOSIS

CASE I° (Unit No. 269182) —The patient was a 49 year old painter, who was admitted to the Albert Merritt Billings Hospital on August 24, 1941. He reported that he had been well until three days earlier when he noted pain in the back of his head and in his neck. During the following night he had several loose stools and on the next day experienced general malaise and felt chilly.

On admission the patient appeared drowsy, but in no acute distress. There was pharyngitis and diffuse abdominal tenderness. The temperature was about 105° F., the white blood count was 15,000. On the second and third hospital day the temperature reached 105° and 104° F., respectively, and the drowsiness and general malaise persisted. On the fourth and fifth days some stiffness of the neck was noted and the patient appeared definitely clouded mentally. He was disoriented and uncooperative, performing continuously restless, plucking movements with his fingers. A coarse, irregular tremor accompanied voluntary movements of the upper extremities, and a plastic "lead-pipe" type of resistance to passive movements in the upper and lower extremities was observed. There was no evidence of paralysis. A lumbar puncture done on the fourth hospital day revealed normal pressure (140 mm.), there were 180 lymphocytes per cmm; the protein content was on the upper limit of normal (49 mg. per 100 cc.), the sugar content (83 mg. per 100 cc.) was not reduced.

The disease reached its peak on the fifth hospital day, from then on, the signs and symptoms disappeared gradually. There was, however, still some tremor and rigidity present when the patient was discharged from the hospital on October 15, but he seemed well on the way towards complete recovery. His serum was found to contain antibodies in high concentration neutralizing the virus of western equine encephalomyelitis, but there was no protection against other viruses that could have produced a similar clinical picture. A diagnosis of "western equine encephalomyelitis" was therefore made.

Disregarding the type of encephalitis present in this case, which could only be identified by proving the presence of specific antibodies, on what grounds should one suspect the diagnosis of encephalitis in

* For further details of this case see R. B. Richter, JAMA, 119:486, 1942.

similar cases, and what procedures are indicated to strengthen the diagnosis?

For the majority of cases a discussion of the following points should be useful (1) the presence of a "flu-like" syndrome, (2) signs of meningeal irritation and mental changes, (3) focal signs and (4) spinal fluid changes

1 The Flu like Syndrome—Fever, malaise, headache pain behind the eyes and with eye movements, also vague muscular and abdominal discomfort, are usually present during the first, prodromal stage of encephalitis. In the abortive cases the disease seemingly ends with this stage

2 Signs of Meningeal Irritation and Mental Changes—Later, signs of mild or moderate meningeal irritation appear: a stiff neck, pain in the back on raising the extended leg of the patient, and Brudzinski's sign (sudden passive flexion of the neck is accompanied by flexion of the knees). It is usually at this stage that the patient shows mental changes, which may range from mild noncooperativeness to confusion and disorientation, and even severe delirium. In dealing with such complications it is best to avoid heavy sedation, especially with the barbiturates which often render the patient more uncontrollable. Physical restraints should be employed if necessary, the patient should be placed in a dimly lit, but not dark, room, and all noise and disturbance avoided. Even seemingly completely irrational patients often become much more quiet when spoken to in a calm and reassuring way, and such simple measures are often the best in dealing with the situation. If sedation must be given, the drug of choice is paraldehyde. It is best to start with at least 12 cc., made palatable by chilling and the addition of orange juice. Giving the paraldehyde by rectum cannot be recommended because the patient usually expels it and, in the struggle, becomes more noisy and uncooperative. Paraldehyde can also be administered by intramuscular injection (6 cc. deep into the gluteal region), but this should be done only when absolutely necessary because of the danger of abscess formation.

3 Focal Signs—Neither the stage of the "flu like syndrome" nor the development of meningeal signs and mental changes is yet definitely suggestive of inflammatory disease of the brain substance. The bacterial meningitides, and in particular tuberculous meningitis, often produce not only stiff neck, pain on straight-leg raising and Brudzinski's sign, but also, because of toxic influences on the brain parenchyma, the signs of toxic encephalopathy, described above as confusion and delirium. In the true encephalitides, however, a number of characteristic "focal" neurological signs and symptoms are often encountered.

Lethargy—On superficial examination the patients, especially in the classic epidemic encephalitis (lethargic encephalitis von Economo's

encephalitis), may appear to be in coma. They can, however, be aroused from their almost continuous sleep and will answer questions, only to fall asleep again in a few seconds as soon as the insistence of the examiner lags. While this kind of somnolence in an otherwise compatible setting should arouse the suspicion that the case in question is one of encephalitis, especially of the von Economo type, lethargy is not per se diagnostic of this disorder but rather indicative of the favorite location of the lesions in this disease. It is the basilar part of the brain which is involved most frequently and, with reference to the symptom of lethargy, particularly the posterior part of the hypothalamus and the gray matter around the Sylvian aqueduct. Brain tumors or metastases anywhere in the cerebral hemisphere can, by increasing the intracranial tension, produce edema and dysfunction of the same regions and so lead to somnolence which is indistinguishable clinically from the one encountered in lethargic encephalitis. Tumors of the basal parts of the brain, e.g., thalamic tumors, will of course be particularly likely to produce this symptom. The differentiation is often difficult for, while, theoretically, the symptoms of a neoplasm should develop and increase gradually, there are some cases in which there is hemorrhage into a tumor which has remained "silent" up to this moment, presenting the deceptive picture of acute or subacute disease. Neither is presence or absence of increased intracranial pressure always of decisive help. Infiltrating thalamic tumors, for instance, may not produce much intracranial hypertension; on the other hand, inflammatory brain disease may, and usually does, increase the spinal fluid pressure and may even produce mild papilledema.

Another condition sometimes, though rarely, gives rise to diagnostic difficulties in regard to the symptom of lethargy and the diagnosis of encephalitis. An acutely developing schizophrenic reaction, especially the catatonic form, can easily be mistaken for the lethargy of encephalitis. A report of previous similar reactions, and the fact that the patient tended to be shy, solitary or otherwise abnormal in his relation with people, will be of help in making the correct diagnosis. The sodium amytal test may be used to advantage, although great caution must be employed in performing it. One-half gram ($7\frac{1}{2}$ grains) of sodium amytal is dissolved in 10 cc of distilled water and slowly administered by the intravenous route while the physician encourages the patient to tell what is going on in him. During the injection, which should proceed very slowly (at the rate of about 0.5 cc per minute), the blood pressure should be continuously checked by an assistant and any drop of more than 20 mm of mercury should be an indication for temporarily stopping the injection. It will soon become apparent during the test whether the patient is emerging from a catatonic stupor and begins to talk of his fears, guilt feelings

or other delusions, or whether the sleepiness increases still further, as in organic damage to the hypothalamic region.

•Eye-muscle Palsies—Like the symptom of lethargy, eye-muscle palsies leading to double vision occur most frequently in the von Economo's encephalitis. Again it must be stressed that this symptom does not necessarily indicate the presence of the ophthalmoplegic variety of this disease. It is rather an expression of the favorite location of its lesions, i.e., in the base of the brain, particularly the diencephalon, and in the mesencephalon, where the nuclei for eye movements are located. Obviously, therefore, not only inflammatory lesions but also tumors or degenerative processes can produce the same symptoms. Infiltrative tumors of the base of the brain and pineal tumors compressing the mesencephalon from above are examples. It might be mentioned here that the least significant eye-muscle paralysis, from the diagnostic standpoint, is that of the lateral recti. The sixth cranial nerves, which supply these muscles, have such a long intracranial course and are therefore subject to damage from so many causes that their involvement often reveals nothing more definite than the presence of organic disease of the brain.

Involuntary Movements and Increase in Muscle Tone—Aside from lethargy and eye-muscle disturbance, there is a host of other focal signs in encephalitis. At the top of the list, mainly as an expression of lesions involving the nuclei of the extrapyramidal system, are involuntary movements and increase in muscle tone. In Case I these consisted of tremor, and the so-called "plastic" or "lead pipe type" rigidity of the extremities. Sometimes one may see choreiform movements or the so-called dystonic turning and twisting motions of head or trunk. Violent involuntary eye movements are rare, more frequent are the slow, writhing contortions, especially of the fingers and hands, which are usually termed "athetoid." Intermittent increase of resistance on passive motion, the "cog-wheel" phenomenon, is another form in which the increased muscle tone may occur.

Among the involuntary movements one might also class the convulsions which sometimes occur in the course of encephalitis. They are, however, essentially different phenomena, due to cortical irritation and not to involvement of the basal ganglia.

Other Focal Signs—That a diffuse inflammatory disease like encephalitis should sometimes produce hemiplegia, hemianesthesia, hemianopia, nystagmus and aphasia is to be expected. But while it is true that now and then these and other symptoms are present, it is rather striking how much rarer they are than lethargy, eye muscle palsies, involuntary movements and increase in muscle tone. The so-called "cortical anesthesia" is often overlooked, it consists of inability to recognize objects by palpation despite preserved touch sensation.

Before discussing the important role which the examination of the

spinal fluid plays in the diagnosis of the encephalitides, two cases will be briefly presented, in both of which, at an early stage, a tentative diagnosis of encephalitis was made.

CASE II (Unit No 287246).—This patient was a 35 year old scientist who was admitted to the Billings Hospital on June 23, 1942. He had come to Chicago only two days before, in order to take part in a scientific meeting. After his arrival in Chicago he was very tired and fell asleep several times during the meetings. On the day before admission he felt particularly worn-out, around noon he fell asleep in a public toilet and remained there, undetected, apparently in a sitting position, for about twenty-four hours. After being found he was awakened with difficulty, looking extremely drowsy all the while. Shortly before he was taken to the hospital he had what was called a "shaking spell."

Upon admission the patient appeared only mildly confused but extremely drowsy. He denied headache but complained of weakness in his right arm. His temperature was 100.8° F, the white blood count 9850. The physical and neurological examination was essentially negative except for absent tendon reflexes in the right arm, and expressions of pain when the neck was flexed passively. The outstanding feature appeared to be extreme somnolence. He would answer a few questions intelligently but seemed to be able to keep awake only with the greatest effort. He fell asleep during his supper, which was especially remarkable in view of the fact that he had had nothing to eat or drink for more than twenty-four hours.

In view of what appeared to be an acute disease with extreme drowsiness, mildly stiff neck, mental confusion, localized weakness of the right arm and the history of an epileptiform seizure, a tentative diagnosis of acute encephalitis was made. A lumbar puncture, however, which was performed a few hours later and which revealed no abnormality of the spinal fluid, made the validity of this diagnosis highly questionable. The fluid was under normal pressure (150 mm) and contained only two lymphocytes per cubic millimeter. The total protein content was 38 mg per 100 cc. (normal 15 to 45 mg 100 cc.) and the sugar content was not reduced (92 mg per 100 cc.). The Wassermann test was negative and the Lange curve 0000000000.

On the following day the behavior of the patient led us to consider more and more a hysterical or schizophrenic reaction. At times the patient was mute and motionless though mostly with his eyes wide open. At other periods he performed stereotyped movements, such as "sitting-up exercises" in bed, which he repeated until the skin of his feet began to show abrasions. He answered to questions in a short, senseless and haughty manner, became negativistic, rejecting food and refusing to submit to such ordinary hygienic requirements as washing. The weakness in his right arm disappeared rapidly. It was probably due to the effect of immobilization and pressure during his prolonged "sleep" in the rest room. He was transferred to a private sanitarium on July 2, 1942, the final diagnosis was "schizophrenia, catatonic type."

Without any further comment on the symptomatology, classification, or pathogenesis of schizophrenia, a further case will be briefly described, and then some important features of the two cases discussed together.

CASE III (Unit No 352151)—The patient, a 20 year old laboratory assistant, was admitted to the Billings Hospital on February 7, 1946. He reported that about one week earlier he had had a headache, especially around the eyes, which lasted for two days. Following this he developed diarrhea which was treated with "powders." He continued to feel poorly, however, and was very sleepy all the time.

On the day of hospitalization he developed unsteadiness and noticed that he was seeing double.

On admission the patient appeared listless, drowsy and confused. His temperature was 100.5° F, his white count 7200 with 50 per cent lymphocytes. There was no neck stiffness but a number of abnormalities in the neurological status most of which were referable to the cerebellar system. The patient showed profound disturbance of standing and walking with tendency to fall backward, ataxia of both arms, and vertical and horizontal nystagmus. There was also diplopia, though without visible strabismus, and apparently some inequality of the tendon reflexes. "Acute nonsuppurative encephalitis" was diagnosed and lumbar puncture advised. As in the preceding case, however, the spinal fluid findings were hardly abnormal. There were no cells and the total protein content of 50 mg. per 100 cc. could at best be considered borderline.

The patient remained in the hospital until the first of March, gradually losing his unsteadiness, nystagmus and diplopia and recovering from his drowsiness. The true story concerning the etiology of his "encephalitis" was learned only one month after his discharge from the hospital when, during a check-up visit at the outpatient department, the patient confessed that he had felt depressed prior to his hospitalization and had taken a "box" of sleeping tablets. The final diagnosis was "acute barbiturate poisoning."

Comment on Cases II and III—In both of the cases just described a diagnosis of acute encephalitis was made on clinical grounds. In both cases this diagnosis turned out to be erroneous, in spite of the application of the criteria already discussed.

1. The presence of a "flu-like" syndrome. In both cases the patients reported that they had felt poorly for several days, in the second case there was a history of headache around the eyes and the presence of diarrhea. In both cases elevation of body temperature on admission was observed, which, in retrospect, seems to have been due to dehydration.

2. The presence of signs of meningeal irritation and mental confusion. Only in the first case did one examiner gain the impression of mild neck-stiffness. Neither patient showed the Brudzinski sign or experienced pain in the back on straight-leg raising. Resistance, therefore, which one encounters when attempting to bend the neck of a noncooperative patient should obviously not be taken as signifying meningeal irritation unless other signs (Brudzinski, Kernig) support this assumption. The mental changes seen in both cases were certainly such as to be easily mistaken for the kind frequently found in the encephalitides. The ability of the schizophrenic patient, however, to answer a few questions intelligently—despite his otherwise grossly abnormal mental state—might have led to a different interpretation of his "confusion."

3. The presence of focal neurological involvement. In the case of catatonic schizophrenia, the combination of somnolence, muscular rigidity, weakness in the right arm and the report of a "shaking spell" suggested lesions in the hypothalamus and the basal ganglia, to account for the first two symptoms and cortical involvement to account for

the monoplegia and the epileptoid attack. In the other case, the sleepiness and the diplopia pointed to the hypothalamus and mesencephalon; the ataxia, toward cerebellar involvement.

4. Spinal Fluid Changes.—Examination of the spinal fluid is of paramount importance in differentiating the encephalitides from toxic encephalopathy in which there is merely toxic-irritative involvement of the brain, as in the delirium of fevers and in various poisonings. It serves also to distinguish encephalitis from states in which no histopathological changes of the brain and the meninges seem to be present, as in schizophrenia. It is also essential, finally, in the diagnosis of primarily meningeal inflammation, particularly purulent and tuberculous meningitis.

In the group of inflammatory diseases of the brain caused, or at least presumably caused, by viruses, the spinal fluid examination should typically give the following picture: initial pressure normal (50 to 150 mm of spinal fluid) or slightly elevated (150 to 250 mm), cell count increased, usually one to several hundred cells per cubic millimeter, cell increase predominantly due to presence of lymphocytes; Pandy reaction positive and total protein content moderately elevated to about 60 or 70 mg per 100 cc (normal 15 to 45 mg per 100 cc.). No micro-organisms should be found on smears or after culturing the fluid (including cultures for yeasts and molds on Sabouraud's medium).

Up to this point it is all too often true that one cannot definitely state whether the case in question is one of tuberculous meningitis or of encephalitis due to virus infection. If tubercle bacilli are found either in smears from the sediment or from the pellicle (stained by the Ziehl-Neelson method), the diagnosis, of course, is established. It is well known, however, how difficult it often is to find tubercle bacilli, even in the most virulent forms of tuberculous meningitis, furthermore, by the time the result of animal inoculation is known the patients with tuberculosis meningitis are often dead. A very helpful aid in the differential diagnosis of such cases is to determine the sugar content of the spinal fluid. In tuberculous meningitis it is often markedly decreased, in the virus encephalitides it is normal. Only on two conditions, however, should a reduced sugar content be accepted as a valid diagnostic criterion. (1) The cell count should not be unduly high. With a severe pleocytosis of, for example, 1000 cells, there is reduction of spinal fluid sugar whether or not the responsible organism is the tubercle bacillus. (2) Simultaneously taken blood sugar levels should be normal or above normal. The sugar content of the spinal fluid, although always less than the blood sugar, rises and falls with the latter. If, however, these two conditions are fulfilled—if for instance with a cell count of 200 or 300 cells and a blood sugar level of 130 mg per 100 cc the spinal fluid glucose is 35 mg per 100 cc. or less—

then the suspicion that the case in question is one of tuberculous meningitis rather than virus-encephalitis should induce a repeated and careful search for tubercle bacilli

PROGNOSIS AND SEQUELAE

Compared to the always fatal outcome of tuberculous meningitis and the usual fatal outcome of deep-seated brain tumors, both of which may resemble encephalitis, the prognosis of the encephalitides is favorable. To make a more specific statement that would have general validity is impossible. All virus (or presumably virus) encephalitides may occur in a fulminant form, leading to death within twenty-four to forty-eight hours, or they may run a very mild, abortive course, which is merely characterized by symptoms of general malaise, headache, fever and the like. The abortive forms are usually not recognized, except when suspected in case of an epidemic and subsequently proved by the presence of a rising antibody titer in the serum of the patient. There is, however, apart from the immediate danger of the acute disease, another factor that has to be considered, especially in the case of lethargic encephalitis the *sequelae*. Of these there are two forms

1. The immediate sequelae are to be understood in terms of irreparable damage done by the acute disease, comparable to the residual paralysis of acute anterior poliomyelitis. Among this group of residuals we may find hemiplegia, convulsions, tremors and other involuntary movements, rigidity, ataxia, intellectual deficit and diabetes insipidus. It is characteristic for this group of symptoms that—like the paralyzes of poliomyelitis—they reach their peak during the acute illness and then begin to improve. At first the improvement is rapid, corresponding with subsiding edema of the brain and return of function in recoverably altered neurons. Further improvement is slow and is probably due mainly to increase of general strength and to the growing ability of the patient to make use of the remaining healthy neuronal and muscular substance.

2. While the immediate sequelae are not of very great importance (they are incomparably less severe than those seen in poliomyelitis), the late sequelae are an always lurking danger, even in mild cases which, as stated above, are often not even recognized as encephalitis. Sometimes directly following the acute disease (but increasing in severity, in contrast to the immediate sequelae), more often after an interval of months or years, the patients begin to show the insidiously progressive disorders which are usually termed postencephalitic or diagnosed as chronic encephalitis. Most often the symptoms point toward involvement of the same regions that were the seat of the acute infection. There are progressive increase in muscle tone, postural changes in trunk and limbs, the development of an expres-

sionless, masklike faeies, and various involuntary movements, predominantly the slow "resting" tremor, all indicating involvement of the basal ganglia and the related portions of the extrapyramidal system. There are also the attacks of involuntary deviation of the eyes, the oculogyric crises, which probably are related to disease of the mesencephalon. Hypersecretion of sebaceous glands may occur also, leading to the development of the "oily faeies." Increased salivation and disturbances of sleep (insomnia, narcolepsy, reversal of normal sleep rhythm), frequently encountered, are the visible expression of damage to the hypothalamic region. Finally, there is a host of other changes, ranging from peculiar tics and spasms to the type of moral and intellectual deterioration which is usually called "personality disorders of encephalitis." The etiology of this progressive symptomatology, frequently occurring long after an acute lethargic encephalitis, poses a challenging problem. Are we confronted simply with a diseased or weakened state of certain portions of the nervous system, with slowly degenerating neurons, comparable to the "abiotrophy" of diseases like paralysis agitans? Or does the original virus infection never clear up completely but continue in an altered, chronic form? No definite answer can be given at the present time, although authoritative opinion seems inclined to consider the second possibility as more likely and therefore calls the condition "chronic encephalitis" rather than "postencephalitic state."

A few words about the differential diagnosis between chronic encephalitis with the symptoms of Parkinsonism and the degenerative disease paralysis agitans, or Parkinson's disease, might be in order. The encephalitic variety is not restricted to the old, on the contrary it seems to occur (or at least be diagnosed) mostly in the younger age groups. Oculogyric crises, vegetative phenomena and sleep disturbances are characteristic of chronic encephalitis, it also shows less complete and more asymmetrical involvement than is usually found in paralysis agitans. Often, quite unlike paralysis agitans, the disease progresses to a point and then becomes stationary. The history of the acute phase of encephalitis is unfortunately not usually helpful in differentiating the two forms. The reason for this is the fact that, especially in recent years, the classic form of lethargic encephalitis has been encountered hardly at all, while the chronic encephalitides are undiminished. The probable explanation for this phenomenon is the occurrence of abortive forms of acute encephalitis, which hide under the clinical picture of "flu," i. e., a disease with fever, headache and muscle pain, to which not much attention is paid at the time but which, perhaps after years, is followed by the development of the Parkinsonian syndrome, oculogyric crises and other encephalitic sequelae.

For the treatment of the Parkinsonian syndrome, stramonium should

be given, either in pills ($2\frac{1}{2}$ grains three times a day) or as tincture of stramonium (15 drops three times a day). As this medication serves merely for symptomatic relief, the evening dose should be taken by the patient several hours before bedtime, otherwise the effect is wasted, for during sleep the tremor disappears spontaneously. Also hyoscine hydrobromide ($\frac{1}{150}$ to $\frac{1}{100}$ grain three times a day) can be given, or combinations of hyoscine and stramonium. To assure maximum relief from the symptoms, the medication should be increased to tolerance, this, unfortunately, is soon reached, for the dryness of the mouth and the blurring of vision which are caused by ingestion of stramonium or hyoscine are quite bothersome to most patients. To diminish the blurring of vision, pilocarpine sulfate (0.5 per cent solution, one drop in each eye, twice a day) can be used to good advantage. The somnolence, and especially the syndrome of narcolepsy, which is characterized by sudden episodes of irresistible sleepiness, are best dealt with by giving benzedrine sulfate. One may start with 5 mg. in the morning and 5 mg. at noon, and later increase the dosage as the case warrants. For some unexplained reason benzedrine occasionally also seems to diminish the number of oculogyric crises.

SUMMARY

1 By "acute encephalitis" is understood a group of acute inflammatory diseases of the brain. Some of them, as the western and eastern equine encephalomyelitides and St. Louis encephalitis, are due to a neurotropic virus. Others, for example, the von Economo type, are presumably due to such a virus.

2 A general outline of the symptomatology for the entire group is given which can be summarized as consisting of a "flu like" syndrome of meningeal irritation and mental changes, the development of focal signs (including lethargy, eye-muscle palsies, involuntary movements and increase in muscle tone), and the presence of changes in the spinal fluid.

3 No attempt is made to distinguish between the various forms of encephalitis, although it is stated that severe lethargy, eye-muscle palsies and involuntary movements are characteristic of the von Economo type. The progressive increase in antibody titer can be used to differentiate between the various forms which are due to different viruses. Serum from the patient should be obtained early in the disease to be compared with later samples for the relative content in antibodies. The performance of these tests is usually the job of the public health authorities.

4 The differential diagnosis is discussed, with special reference to deep lying brain tumors, schizophrenia, barbiturate poisoning, tuberculous meningitis and some other diseases.

5 The prognosis and treatment of the late sequelae, the so-called "chronic encephalitis," are also dealt with.

RHEUMATIC FEVER IN THE ADULT

DAVID H. ROSENBERG, M D °

UNTIL recently the occurrence of rheumatic fever in the adult received little or no consideration in the differential diagnosis of febrile illnesses. Outbreaks of acute rheumatic fever among members of the Armed Forces served to direct attention to its appearance in adults, particularly in the younger age group, and to the importance of its early recognition. In this presentation, I shall confine myself to the observations which were made on a large group of adults, ranging from 17 to 41 years of age.

ETIOLOGY

The etiology of rheumatic fever must still be regarded as obscure. From the numerous epidemiologic studies, however, it is apparent that there exists a close relationship to epidemics of Group A beta hemolytic streptococcus infections. Thus, in almost all patients one can elicit a history of an acute upper respiratory infection, such as coryza, sinusitis, pharyngitis, tonsillitis or otitis media, which had occurred one to four weeks prior to the onset of the attack of rheumatic fever. At times, scarlet fever may precede an attack of rheumatic fever. Exercise, fatigue, and damp, rainy or cold weather appear to act as provocative factors. As in many other acute febrile diseases, a distinct seasonal variation may be noted, the highest incidence occurring during the winter months. In 38 per cent of the patients, an antecedent history of rheumatic fever, chorea or growing pains may be elicited. In many instances a familial history of rheumatic fever is obtainable, a fact which emphasizes the importance of a constitutional factor.

The recent experimental studies of Rich and Gregory¹ are of considerable interest and suggest that the lesions of rheumatic fever are due to hypersensitive reactions. This view is based on their finding of lesions similar to those of rheumatic carditis and pneumonitis in rabbits subjected to anaphylactic "serum sickness."

SYMPTOMS AND PHYSICAL FINDINGS

Contrary to general belief, the clinical manifestations of rheumatic fever may be extremely varied and even bizarre. In most instances, the onset is heralded by the appearance of acute articular pain, swell-

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ing, stiffness, tenderness and often redness of one or more joints. The knees, ankles, wrists, elbows and small joints of the feet are most frequently affected. These symptoms are accompanied by malaise, lassitude, fatigue and tachycardia, with fever varying from 99° to 104° F. Although, characteristically, other joints become involved in a migratory arthritis, the initial joint changes often persist while other joints become successively affected. It is common to observe marked distention of the knee joints with synovial fluid. Drenching sweats are observed very infrequently and in this respect rheumatic fever in adults differs from the acute disease in childhood. Epistaxes may appear early but should not confuse the picture. In some patients, however, only mild pain and stiffness of a single joint may be noted, objective findings, systemic manifestations and tachycardia being absent. In others, the local articular findings or redness, tenderness and swelling are minimal.

In a small group of patients, vague muscular pains and stiffness may be the only symptoms. In another group, chills and fever are the only presenting complaints. Lumbar backache occurs frequently and is often accompanied by urinary frequency and by the microscopic findings of pyelonephritis.

It is of particular importance to recognize those instances in which the presenting symptoms are abdominal, for they may simulate the clinical picture of acute appendicitis. These symptoms consist of abdominal pain, anorexia, nausea, vomiting and at times diarrhea. Diffuse abdominal tenderness with or without the rebound phenomenon is commonly found. However, a careful history together with close clinical observation will reveal the coexistence of joint pain, tenderness and stiffness and evidence of acute carditis.

In some patients the principal symptoms are precordial pain and dyspnea with or without cyanosis. In these instances, joint manifestations though present are minor and are generally disregarded by the patient. Electrocardiographic tracings made on these patients reveal evidence of myocardial damage with varying degrees of auriculo-ventricular block, sometimes progressing to complete heart block with ventricular rates as low as 20 per minute.

Cerebral manifestations may also appear, but are usually mild and consist mainly of drowsiness and stupor. In the acutely ill patients with high fever, transient psychoses with delirium may develop. Unlike rheumatic fever in childhood, the disease in adults is very rarely accompanied by chorea. In patients with stiffness and pain in the cervical spine, meningitis may be closely simulated but this manifestation is rarely encountered.

In only a small percentage of patients is a perceptible increase in the size of the heart observed during the first attack of rheumatic fever, and in the majority of these the enlargement is slight unless

complicated by acute pericarditis with effusion. It will be noted, however, that the first sound at the mitral area frequently becomes muffled or diminished in intensity. In most cases, a soft blowing systolic murmur develops at the mitral area. In many of these, it becomes audible over the entire precordium, in others, it is loud and harsh and is transmitted to the axilla. Such murmurs often vary in intensity from day to day and may disappear when the patient assumes the sitting posture. They are usually produced by relative dilatation of the mitral orifice rather than by verrucose vegetations on the valves.

A low-pitched, rumbling mid-diastolic murmur may appear at the mitral area within two or three months after the appearance of acute rheumatic fever. This murmur may be elicited best during forced expiration with the patient lying in the left oblique position. Although this murmur may on rare occasions disappear completely within four weeks, it generally persists and may be regarded as positive evidence of involvement of the mitral leaflets.

The aortic second sound may become slurred and a soft, blowing diastolic murmur may appear at the left third and fourth interspaces near the sternum. The latter finding is an early indication of involvement of the aortic leaflets. Only in the more advanced cases of aortic insufficiency does the diastolic murmur become audible at the aortic area. Later, peripheral signs of aortic incompetency may be noted. The murmur of early aortic insufficiency may ultimately disappear, but this occurs so rarely (0.8 per cent) that for clinical purposes it may be regarded as indicative of aortic endocarditis.

Although involvement of the heart in rheumatic fever may be manifested by clinical evidence of myocarditis and endocarditis alone, anatomic studies show that it is in reality a pancarditis. The clinical signs of acute pericarditis may be recognized in only a small number of patients, either by the finding of a to-and-fro pericardial rub or by the presence of pericardial effusion. Electrocardiographic studies alone may reveal the presence of an otherwise "silent" pericarditis. In those patients with manifest evidence of acute pericarditis, rheumatic pleurisy with or without effusion, and rheumatic pneumonitis must be sought for.

Skin lesions when present are usually those of erythema multiforme but in some patients ecchymotic areas may be noted particularly at the site of the affected joints, spreading to involve the other parts of the extremity. In contradistinction to rheumatic fever in children, subcutaneous nodules are rarely, if ever, found in the adult patient.

Enlargement of the spleen in rheumatic fever is an extreme rarity (0.5 per cent) and when found clinically is only slight. The presence of an enlarged spleen must, therefore, raise the question of some complication, notably thrombolytic endocarditis.

As in other acute systemic infections, rapid loss of weight, amounting to as much as 20 pounds, occurs almost invariably during the acute stage of the illness.

The incidence of electrocardiographic abnormalities varies with the frequency with which serial electrocardiographic studies are made. Electrocardiographic changes were noted in 63 per cent of our patients, often after only a few days of illness. The most frequent abnormality is prolongation of the auriculoventricular conduction time. It must be emphasized that, although the P-R intervals may be within the range of normal (0.12 to 0.21 second), repeated electrocardiograms may show variations in excess of 0.02 second. Such variations are significant of first degree auriculoventricular block and indicate the importance of frequent electrocardiograms. All degrees of auriculoventricular block and occasionally that of the indeterminate type may be observed. The QRS complexes may become inverted and notched in the chest leads, and the S-T segments may be either elevated or depressed beyond normal in one or more leads. The T waves frequently become tiny, diphasic or inverted in one or more leads, especially in the chest leads. In patients with signs of pericarditis, the T waves usually become inverted in the limb leads, S-T changes may be slight. Premature systoles appear frequently but paroxysmal auricular tachycardia, auricular fibrillation and auricular flutter occur very rarely. These various electrocardiographic abnormalities are transient in almost all cases and usually disappear within seven to twenty-one days.

In almost all patients the sedimentation rate is increased, but in the exceptional case with mild joint involvement and electrocardiographic evidence of first degree auriculoventricular block, it may be repeatedly normal. Hence, a normal sedimentation rate does not preclude the presence of low grade active rheumatic fever, and must be interpreted with caution.

The blood count usually shows a leukocytosis ranging between 10,500 and 16,000 per cubic millimeter, and in the more acutely ill patients a mild hypochromic anemia. Albuminuria, pyuria and microscopic hematuria are frequently present at the onset and generally disappear within a few days.

COURSE

The course of rheumatic fever in adults like that in children is variable. The majority of patients recover after a single bout of fever but in the others the acute stage is followed either by long periods of low grade activity or by remissions and relapses. The danger of disabling heart disease lies chiefly in those cases which follow one or the other of the latter courses. Relapses generally follow hemolytic streptococcus infections of the upper respiratory tract. In eradicating

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foci of infection, attention should also be directed to the paranasal sinuses

DIAGNOSIS

The diagnosis of rheumatic fever may be made without difficulty when acute migratory polyarthritides is associated with acute carditis, electrocardiographic abnormalities, leukocytosis and an increased sedimentation rate. Unfortunately, however, many patients do not present this combination of findings and in these the diagnosis may be most perplexing. It is evident from the foregoing picture that rheumatic fever may simulate many diseases. The possibility of rheumatic fever must therefore receive consideration in all patients with fever accompanied by either arthralgia, muscular pains and stiffness, precordial pain and dyspnea, acute abdominal symptoms or acute pyelonephritis, in whom the diagnosis is in doubt, as well as in those patients with fever of unknown origin.

It should be pointed out that no specific diagnostic test for rheumatic fever exists today, thus necessitating careful and prolonged clinical observation in these cases. Errors in diagnosis are most likely to occur in the milder forms of acute rheumatic fever, in which arthralgia and low grade fever are the main symptoms. A history of antecedent rheumatic fever or chorea may be regarded as highly significant. A familial history of rheumatic fever may be of some help and should receive consideration. Electrocardiographic changes, particularly prolongation of the P-R interval, are to be considered as strong evidence in support of a diagnosis of rheumatic fever, provided other infections which produce similar changes, such as pneumonia, diphtheria, epidemic parotitis and German measles (Rosenberg²) are excluded.

The occurrence of systolic murmurs per se cannot be regarded as of diagnostic value for they may occur in the course of any acute infectious disease. But the development of diastolic murmurs at the left third interspace near the sternum or at the aortic area, mid-diastolic murmurs at the mitral area (in the absence of aortic regurgitation) or signs of acute pericarditis may be considered as confirmatory. Determination of the antistreptolysin titer may be helpful, but only as an indication of a recent hemolytic streptococcus infection. In doubtful cases, the absence of antistreptolysins tends to exclude the diagnosis of acute rheumatic fever.

Differential Diagnosis.—*Acute rheumatoid arthritis* is most frequently confused with rheumatic fever. It may be differentiated by the persistent periarticular swelling of the small joints, its predilection for the proximal interphalangeal joints of the fingers (Haygarth's nodes) and by the usual absence of cardiac involvement. *Gonococcal arthritis* may be recognized by the recovery of the specific organism from the joint fluid. The finding of gonococci in the genitourinary tract in a patient with a recent history of gonorrhea may be regarded

as presumptive evidence of gonococcal arthritis, while a positive complement fixation test per se adds confusion to the diagnosis and is an unreliable diagnostic aid. *Septic arthritis* and arthritis secondary to other acute infectious diseases may be suspected from the antecedent history of infection and from the concomitant disease. *Undulant fever* is usually associated with articular involvement and may be identified by the finding of specific agglutinins in the blood serum in high titer, by intradermal skin tests, or by positive blood cultures. The premeningeal stage of *acute meningococcemia*, when accompanied by acute arthritis may resemble acute rheumatic fever very closely, but it may be differentiated by the history, the presence of a generalized petechial eruption and by corroboratory bacteriologic studies. *Acute gout* at times masquerades as rheumatic fever, but in these instances the hyperuricemia, roentgenographic findings in the bones, and the prompt response to colchicine leave little doubt as to the correct diagnosis. Other diseases, such as *periarthritis nodosa* and *disseminated lupus erythematosus*, may require differentiation, but they are far less frequent than those just discussed.

TREATMENT

The treatment of rheumatic fever consists of complete bed rest, sodium salicylate, 8 to 10 gm daily with sodium bicarbonate, 6 to 8 gm daily, a high calorie, high vitamin diet and codeine sulfate, 0.033 gm, when indicated for severe joint pains. For patients with gastric distress, sodium salicylate, 4 gm in 120 cc. of starch solution, may be administered as a retention enema four times daily. In others, amidopyrine 0.067 gm., or acetylsalicylic acid, 1 gm may be given instead of enemas. When amidopyrine is administered, the leukocyte count should be followed closely. After the articular symptoms have subsided and the sedimentation rate has returned to normal (usually within two weeks) the dosages may be reduced by one-half and continued thusly for one month. It is essential that all patients remain in bed for at least six weeks, and that the temperature, pulse, sedimentation rate and leukocyte count return to normal before the patient may be permitted out of bed. Further, it is advisable to maintain bed rest for four to six weeks after the electrocardiogram has become normal. The period out of bed should be increased slowly and physical activities must be graduated, particular attention being devoted to the pulse rate.

Intravenous 1 per cent sodium salicylate in isotonic saline solution (Coburn)² may be administered slowly in amounts of 1000 to 2000 cc. daily to the acutely ill patients and to those refractory to or showing gastric intolerance to oral therapy, maintaining a blood salicylate level of at least 350 micrograms per cubic centimeter, until the patient is asymptomatic and until the sedimentation rate has dropped 20 per cent. Although relief of symptoms may be obtained more rapidly by

this method, nausea, vomiting, tinnitus and deafness occur frequently, and marked cerebral symptoms in the form of delirium and stupor may develop occasionally. This form of therapy should, therefore, be employed with caution and only in selected cases.

I have used both sulfadiazine and penicillin in the treatment of acute rheumatic fever but have observed no beneficial effects. On the contrary, the polyarticular symptoms have become intensified during sulfadiazine therapy. Whether any untoward cardiac effects result from sulfadiazine cannot be stated with certainty at this time.

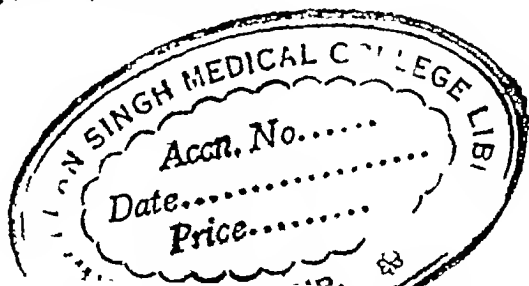
Digitalis need be employed only in those patients with congestive heart failure, in those with a persistent tachycardia of 125 or more and in those with auricular fibrillation and flutter. Acute pericarditis with effusion should be treated conservatively and without aspiration of the pericardial sac, inasmuch as massive effusion occurs very rarely in rheumatic fever. Similarly, pleural effusion need not be treated by thoracentesis except in patients with marked respiratory embarrassment.

During the convalescent period, some patients may be troubled with residual stiffness and mild aching in the joints, especially during cold or damp weather. In many of these, diathermy, massage and whirlpool baths have proved beneficial.

In an effort to prevent recurrences of rheumatic fever, studies have been conducted by Thomas and associates,⁴ Coburn,⁵ and Holbrook⁶ on the prophylactic use of sulfonamide drugs. Their observations indicate a reduction both in the incidence of hemolytic streptococcus infections and in the recurrence rate. While their results seem promising, further well controlled studies are necessary to determine the efficacy of this approach.

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PEPTIC ULCER

LEE C. GATEWOOD, M.D., F.A.C.P.*

In the years that have passed since Sippy first described his method of ulcer treatment in 1915 there have been many changes in point of view and many new technics have been added. There was a time when medical society programs frequently headlined such symposia as "Medical versus surgical treatment of ulcer" and there ensued a lively controversy over who should have the honor and responsibility of saving the patient. Through the years, however, a high degree of cooperation has developed between internist and surgeon in the care of these patients and sometimes now presents almost an Alphonse and Gaston situation with each urging the other to take over.

ILLUSTRATIVE CASES

The following group of patients has been selected as presenting examples of some of the problems commonly met in the treatment of peptic ulcer. It cannot be too often emphasized that each patient is an individual and presents an individual problem. When one finds in the clinical record the statement, all too often encountered, "the patient was put on routine ulcer management," one may thereby recognize an invitation to therapeutic failure.

CASE I.—Mr. G. C. H., aged 56, executive in a large corporation with international interests. In 1935 the patient first experienced epigastric distress occurring regularly about two hours after eating, relieved by food or alkali, which he continued to use on his own initiative for the next two years during recurring periods of distress. In 1937, while on a business trip to Europe, he had an unusually severe attack and was hospitalized for one week in Paris and advised to return to the United States for further examination and treatment. During the next two or three years duodenal deformity was repeatedly reported on fluoroscopic examination. Treatment during this period consisted, for the most part, of a bland diet with milk between meals during periods of distress. Alkali was used only when distress was present. The patient usually had two or three drinks of Scotch whiskey per day and tobacco was used "in moderation." In October 1943 the patient experienced his first hemorrhage and at that time was hospitalized for six weeks and had two blood transfusions. Again in December 1945 while on a train enroute to California, the patient experienced sudden faintness, weakness, nausea and pallor. He was examined by a physician on the train and on arrival in Oakland was removed to a hospital where he was again treated with a milk and cream diet, bland foods and aluminum hydroxide.

The patient presented himself for examination two months later having had no digestive distress since his recent period of hospitalization. Examination showed a

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large, well nourished and apparently vigorous man of aggressive driving type and with no abnormal physical findings except for a moderate enlargement of the heart with no evidence of cardiac insufficiency. The liver was barely palpable. No abnormal masses were palpable in the abdomen and there was only slight epigastric tenderness and no abnormal muscle defense reaction. Blood pressure was normal. Blood counts were within normal limit and urine findings were normal. X-ray findings include a marked deformity of the duodenal bulb with considerable spasm. No crater was demonstrated. Stool examination at this time was negative for occult blood.

The problem presented by this patient is that of the high-tension, hard-driving type of individual whose business takes him to many places where it is, to say the least, difficult to carry out any strict program of treatment, that of a man who is impatient of limitations and restrictions, yet who fears the possible serious consequences of an ulcer hemorrhage under unfavorable circumstances. He has never carried out a program of medical management either long enough or accurately enough to determine whether or not a cure could be accomplished by medical means, and it is questionable whether he could be counted upon to do so. Operation is therefore advised with the choice of measures lying between resection and a vagus section of the Dragstedt type.

CASE II—Mrs F. K. was first admitted to the Presbyterian Hospital on September 18, 1924, on another service, with the diagnosis of duodenal ulcer with hemorrhage, old rheumatic endocarditis with aortic and mitral valvular lesions. The patient, at that time a housewife of 34, gave a history of abdominal distress following meals, intermittently for a period of one year, and of pallor, weakness and melena for the previous five days. There is in the record very little information concerning the incidents preceding hemorrhage. The patient remained in the hospital for a period of two months. On admission the blood count showed the hemoglobin to be 28 per cent, red blood corpuscles 2.41 million and leukocytes 9100. At the time of discharge the hemoglobin was 40 per cent and red blood corpuscles 3.93 million.

Following discharge the patient was on a rather rigid dietary regimen for a year and thereafter began to eat—and occasionally drink—as she pleased. She remained free from distress until the early summer of 1927 when she again began to have distress which occurred regularly two to three hours after meals and in all respects conformed to the pattern of a chemical type distress. She was admitted to this service on August 17, 1927, with a history of weakness, faintness and black, tarry stool earlier in that day. The blood count was hemoglobin 68 per cent and red blood corpuscles 2.81 million. Specimens of feces gave positive reaction for occult blood. Two weeks later, when the patient's condition had improved sufficiently to permit fluoroscopy, a typical duodenal deformity was seen. Improvement on Sippy type ulcer management was satisfactory and the patient left the hospital at the end of a month to continue this type of ulcer treatment. It is noted in the summary on discharge that in spite of the fact that motor test meals passed in normal time, the quantity of night secretion was excessive, requiring nightly aspiration to control. The quantity at night aspiration was frequently as much as 500 cc. and on titration showed total acidities varying from 90 to 114, but with no free acid. Operation was considered at this time but was refused by the patient and was not urged because of the heart lesion and because in the absence of demonstrable obstruction on test meals it was felt that the operation of choice should be some type of resection.

During the next eight years the patient had six periods of hospitalization, five of which were initiated primarily for treatment of ulcer or its complications. One hospital admission in 1932 was upon the gynecological service for treatment of menorrhagia, and after operation the patient experienced a recurrence of ulcer symptoms and a moderately severe hemorrhage. Surgical therapy for ulcer mean time included a posterior gastroenterostomy in 1931 with subsequent development of gastrojejunal ulcer and hemorrhage either from this source or from the duodenal ulcer which also showed evidence of recurrence.

The patient's final hospital entry was on November 10, 1935, because of recurrent epigastric distress and recurrent hemorrhage. Fluoroscopic examination at this time showed evidence of both duodenal and gastrojejunal ulcer. Feces were persistently positive for occult blood and blood hemoglobin was 85 per cent and red blood corpuscles numbered 3,890 million. On December 2, 1935, the patient was again operated upon with resection of the two ulcers, closure of the previous stoma and a Polya type of anastomosis. It was recorded at the time of the operation that the closure of the duodenal stump was unusually difficult and an omental tab was sutured to the line of closure as an additional protection. The patient nevertheless had a great deal of postoperative nausea, vomited repeatedly, developed peritonitis and died on the fifth postoperative day. Autopsy revealed no additional facts of importance.

Thus reads the coldly scientific record of the case. The human side of the story, from the viewpoint of psychosomatic medicine, is just as significant. The background of the first two episodes is not recorded. One early attack occurred in a sequence of family financial difficulties during the market crash of 1929. The patient's husband had just lost his position along with his life's savings which had been put into stock of the company, bought on time payments and wiped out in the crash. Another occurred when the patient's father developed an illness diagnosed as carcinoma of the larynx. He was treated with radium with satisfactory results for several months but another episode followed when he required an emergency tracheotomy and still another when he died. When her oldest daughter was married she managed to survive the wedding festivities but had a hemorrhage ten days later. She had another flare-up when the first grandchild was born. It was apparent that throughout the years a period of increased emotional tension was pretty sure to be followed by a recurrence of ulcer activity and very shortly by hemorrhage.

CASE III—Mr. T. G., a young man of 22 years, was discharged from the army following a gastric hemorrhage characterized by hematemesis and melena which occurred on a train en route from his point of induction to the camp to which he had been assigned. He gave a rather vague history of previous epigastric distress, never very severe and not previously sufficient to interfere with his activities or cause him to seek medical advice. He had been a student in an Eastern university at the time he was called for induction and acknowledged a considerable degree of anxiety over leaving college and entering service. Upon the occurrence of the hemorrhage he was immediately hospitalized and fluoroscopic examination disclosed a typical deformity of the duodenal bulb.

After a short period of hospitalization and his subsequent discharge from the service the patient returned to his home. He was employed for a time as a salesman but found the work distasteful and complained of the difficulty in carrying out

dietetic instructions while traveling under wartime restrictions. After a time he reported the recurrence of epigastric distress and subsequently an episode of weakness and faintness, probably signaling a moderate hemorrhage. Re-examination showed duodenal deformity with a marked degree of spasm.

Neuropsychiatric investigation at this time revealed a group of emotional conflicts dating from boyhood and including a sense of inadequacy and especially of inferiority to a brother and sister. He had a distaste for the business in which he was engaged and in which his father held an outstanding position, and a strong desire to leave his home and job for a life at a hunting and fishing resort in the north woods where he had formerly been employed as a guide and had formed a strong attachment to the daughter of the owner of the camp.

CASE IV—Miss Rita M., aged 60, gave a history of recurring attacks of abdominal distress for the past seven years, at first readily controlled by dietetic restriction but gradually becoming more severe and more difficult to control. She was first admitted to the hospital two years ago and at that time obtained complete and immediate relief on hourly feedings of milk and cream, with alkali powders between feedings. Fluoroscopy at that time showed deformity of the duodenal bulb with moderate degree of spasm but with no evidence of actual obstruction. Motor test meals showed no retention.

The patient progressed uneventfully on ulcer management and remained free from distress until three months ago when she again began to have epigastric distress, relieved by food or by alkali or by aspiration of stomach contents, a procedure which she had learned at the time of her previous hospitalization. The distress gradually increased in severity and during the past three weeks she had been reportedly awakened in the night by distress and had obtained relief only by aspirating the stomach contents at such times. She had lost 12 pounds in the past three months.

Roentgenologic examination again showed duodenal deformity but with only a moderate degree of spasm. Motor meal showed retention of 150 cc. of food and secretion at the end of seven hours. Inasmuch as she had repeatedly expressed violent objections to operation she was again started on a strict schedule of ulcer treatment with hourly feedings of milk and cream, alkali between feedings and evacuation of the stomach contents each night at bed time. However, on this regimen she was repeatedly awakened by distress occurring a few hours after retiring. Aspiration at such times showed 150 to 200 cc. of acid gastric secretion. It was evident, therefore, that the quantity of night secretion was sufficient to cause distress and to interfere with healing during the night-time.

Under such conditions one may choose between various regimens for the control of the night secretion. It is readily accomplished by the use of an indwelling tube and continuous drip of a mixture of food and alkali throughout the day and night as advocated years ago by Einhorn and more recently by Winkelstein¹ and associates. For this purpose the food mixture consists usually of milk and cream, supplemented by other food materials which may be included in liquid form and mixed with the alkali necessary to neutralize whatever acid may be secreted in excess of that which will combine with the protein in the food mixture. Insoluble alkalies which cannot readily be kept in

solution or suspension are manifestly not suitable. Those most commonly used are sodium bicarbonate or colloidal suspensions of aluminum hydroxide, each of which has its advantages and its objections.

Another method, and the one adopted in this case, consists in following one of the usual plans of oral feeding and medication during the day, aspirating the stomach content at bedtime as previously and at that time inserting a Levin tube into the stomach. This tube is attached to a Wangensteen aspirator or any other convenient device for continuous suction. An electric pump with intermediate bottle as used in certain types of chest aspiration will serve very conveniently. For purposes of observation it is desirable to measure and send to the laboratory as separate specimens the aspirated secretion of the first three hours and that of the remainder of the night. In those cases which respond favorably, the quantity of secretion in the latter part of the night decreases rather rapidly while that of the early part of the night diminishes more slowly. Our patient obtained prompt and complete relief from her distress with the night aspiration but on two or three occasions when the tube became blocked or the aspirator was not functioning properly she had an immediate recurrence of night distress but was relieved as soon as the aspirator was again functioning. However, although there was considerable variation in the quantities aspirated from night to night, the total volume for the night varying continually from 500 to 1000 cc., the acidities on titration were consistently high and there was no definite decrease in the average quantities for the latter part of the night. Surgery was therefore again advised.

The pattern of night secretion conforms to that which Dragstedt² has described in his studies on the effects of vagus section, and from the evidence thus far available this type of operation may be expected to influence favorably such pathological secretion. It is to be anticipated, however, that a patient of this type after vagus section would show more marked evidence of retention. An operation for the relief of obstruction should therefore precede or coincide with vagotomy if the latter is to be considered. The results thus far reported from vagus section by the subdiaphragmatic approach have been less satisfactory than those from section by the thoracic route. The abdominal route provides opportunity for direct examination of the ulcer and correction of obstruction when present. It makes possible resection when that is deemed desirable on the basis of exploratory findings, and it is to be hoped that further experience will develop a technique for vagus section from below to give satisfactory results and obviate the necessity for the dual approach.

CASE V.—Mrs. B. D., aged 55 entered the hospital May 25 1944. She stated that she had been in good general health throughout her life except for recurrent "sick headaches" which had usually been relieved by inducing vomiting. Weight and

strength had been normal up to eight months previously and she had been in the habit of working hard. At that time she discovered a mass in the suprapubic region and upon consulting her local physician a hysterectomy was advised and was done. Following operation she began to lose weight and to complain of a variety of vague pains and aches but did not at any time complain of abdominal distress recurring with a definite relation to food-taking. Nausea, vomiting and anorexia became frequent and the patient had lost 25 pounds in weight in the past eight months.

Examination showed a markedly emaciated woman of 118 pounds with marked tremor, tachycardia and a basal metabolic rate of plus 63 per cent. Blood hemoglobin was 11.2 gm. and red blood corpuscles 3.22 millions with poikilocytosis and anisocytosis. Gastric analysis repeatedly gave low acid values, the highest being 16 units. Upon stomach fluoroscopy an exceptionally large crater was seen on the lesser curvature of the stomach just above the angle. There was little induration about the crater and the duodenal cap filled normally. Roentgenologic examination of intestine and gallbladder were negative.

Because of the seriousness of the patient's condition and because the findings, though suspicious, seemed more indicative of ulcer than of carcinoma, frequent feeding of milk and cream, supplemented by a high vitamin intake and liver extract were started. The administration of Lugol's solution was also begun at once, with the result that her metabolic rate decreased rapidly to plus 37 per cent, where it remained fairly constant for a time. She was then given thiouracil and the rate and clinical manifestations progressively improved. Meantime there had been a rapid improvement also in the appearance of the gastric lesion on fluoroscopic examination, so that on the twenty-fifth day after the initial fluoroscopy the roentgenologist reported "no evidence of previous gastric ulcer." Throughout the greater part of this period the dietary management had consisted of frequent feedings during the day but with only two or three doses of alkali (aluminum hydroxide) given during the evening after the last feeding. Because of the low acidity of the gastric content the protein in the diet had been adequate to combine with all of the hydrochloric acid secreted during the day. It is to be noted, however, that as the patient's general condition improved her gastric secretion also increased and later analyses showed acidities within the lower limits of normal.

The patient returned for re-examination on January 7, 1946, complaining of distress across the upper abdomen occurring usually in the afternoon or evening. She had not tried the effect of food or alkali upon this distress. In the light of the researches of Ivy³ upon the effect of caffeine upon gastric secretion and upon the activation of ulcer symptomatology, it is interesting to note that she had been drinking 7 or 8 cups of coffee a day. Fluoroscopy showed a crater from the lesser curvature of the stomach with base about 1 cm. in diameter and protruding about 1 cm. from the curvature of the stomach. The duodenal cap filled smoothly. Gastric analyses showed no free acid but total acidities ranging from 21 to 92, with large amounts of mucus present and tests for occult blood positive. Gastroscopy on January 12, 1946, revealed an ulcer on the lesser curvature, its base depressed and its margins slightly rounded, raised and hyperemic. The ulcer defect was recorded as about 1 by 1.5 cm. in diameter and there was a slight nodular elevation at its upper margin. Scattered throughout the rest of the mucosa of the stomach were small acute submucous hemorrhages. The impression of the gastroscopist was of early malignancy.

Laparotomy was performed on January 17, 1946, and a gastric resection was done. Several enlarged lymph nodes were found along the lesser curvature, most of them about the size of a cherry. Following the resection a gastrojejunal anastomosis was performed. The patient made an uneventful recovery. The pathologist made a thorough examination of the tissue removed, including sections through the floor of the ulcer and sections of the lymph nodes removed. The diagnosis was "chronic gastric ulcer, sarcoid-like reaction in lymph nodes." No evidence of carcinoma was found in any of the sections.

CASE VI—Mrs M F, a housewife, was first admitted to the hospital in December, 1944, complaining of epigastric distress intermittently over a period of fifteen years but more severe during the last two years. Fluoroscopy at that time revealed a large crater on the posterior wall of the stomach near the lesser curvature and deformity of the rugae in this region. Gastric analyses gave widely varying results with free acid low and total acidities varying from 20 to 95. The high combined acidity was explained by the presence of large amounts of mucus in the gastric content. The patient's distress disappeared promptly on frequent feedings and alkali of which only small doses were required to control the free acidity. The ulcer crater decreased rapidly in size and disappeared completely within a period of two months.

The patient was a highly emotional French woman and somewhat impatient of restrictions. Her anxieties during this period over the progress of the war in Europe and the fate of friends and relatives there, certainly did not facilitate her medical management and may well have played a part in the course of her disease. However these factors would seem to be beyond therapeutic control. Within a few months she was again complaining of upper abdominal distress and fluoroscopic examination showed the ulcer crater to be again present, in the same location and of about the same size as on the original examination. Operation was therefore advised and on July 29, 1945, a gastric resection was done with Polya type anastomosis. It was recorded at operation that there was no area of thickening on the posterior wall of the stomach approximately 5 by 5 cm. in area and 1 cm. in thickness. Sections made from three different areas showed extensive fibrosis and heavy infiltrations of lymphocytes. The pathological diagnosis was chronic gastric ulcer with extensive inflammation of the stomach wall. Upon the request of the surgeon a considerable number of additional areas were sectioned and in one area only were found epithelial changes compatible with a diagnosis of carcinoma.

Cases V and VI present some of the problems encountered in the management of gastric ulcer, as contrasted with duodenal lesions. They illustrate the rapidity with which ulcer craters commonly heal on acid-control therapy, and the tendency to recurrence. In both instances the mucosa of the resected portion showed evidence of gastritis, and it seems probable that profound malnutrition and vitamin deficiency were important factors in Case V. Both cases illustrate the old maxim that whenever there is reasonable ground to suspect carcinoma a laparotomy should be done. It is in this group of patients that gastroscopy is particularly important, but it must be remembered that in the light of our present knowledge the conclusions from gastroscopy are not necessarily final. In Case V, which was regarded as probably carcinomatous on the basis of gastroscopic findings, no evidence of neoplasm was found, and in the other it proved to be present in sections but certainly could not have been diagnosed gastroscopically.

CASE VII—Mr C. R. aged 53, an executive in a chemical plant, gave a history of recurring distress typically chemical in pattern for a period of several years. In 1943 a subtotal gastric resection was done and for the next few months he remained free from symptoms. He then began again to have epigastric distress, severe and cramping in character and frequently radiating to the back. During the daytime it was readily relieved by food or by alkali and he was thus able to maintain a fair degree of comfort, but he was repeatedly awakened at night by this type of pain.

The initial gastric analysis showed free hydrochloric acid 6 and total acidity 14. Fractional gastric analysis with histamine gave maximum acid values of 38 for free hydrochloric acid and 51 for total acidity. Fluoroscopic examination showed a stomach modified by resection with Polya type anastomosis and with some spasm at the stoma. No ulcer crater could be demonstrated on repeated examination.

This is one of the types of ulcer that is likely to prove unusually resistant to therapy. It is recognized that the most satisfactory results from resection are obtained when, after operation, gastric analysis shows no acid secretion, and that those patients who develop ulcers after resection are resistant to medical management and their ulcers are prone to recur. This patient was, however, extremely loath to undergo further surgery. On medical management of the frequent feeding type he was completely comfortable during the day but almost regularly had distress two or three hours after retiring. Aspiration at such times obtained only small quantities of secretion but gastric lavage would give immediate and complete relief. It was evident therefore that even a small quantity of night secretion was enough to come in contact with the ulcer, to cause distress and presumably to interfere with healing. This is the kind of situation which can best be controlled by continuous drip-feeding. In this way the ulcer can be protected throughout the day and the night and the maximum benefit obtainable from any medical regimen thus accomplished. However, it is questionable whether this patient will be willing to carry out such a program for a time long enough to accomplish thorough healing, and there is no assurance against later recurrence. This patient's problem is therefore one of those best met by additional surgical therapy which might consist of either a further resection or vagectomy.

TREATMENT OF PEPTIC ULCER

Certain basic principles of treatment are generally accepted and one of these is that there should be no such thing as "routine ulcer treatment." Each patient presents individual problems and the treatment should be that designed to meet these problems.

Acid Neutralization.—It is generally agreed that hydrochloric acid secretion plays an important part in causing ulcer and interfering with its healing. The principles of acid control as originally outlined by Sippy still hold good. My experience of several years as consultant gastroenterologist at one of the major diagnostic centers of the Veterans' Bureau, reviewing patients referred from throughout the area from the Allegheny to the Rocky Mountains, served to impress upon me the fact that many clinicians have lost sight of the basic principles outlined by Sippy. When a patient admitted to the center stated that he had been on "Sippy treatment" it might mean only that he had had some milk in his diet and had been given some alkali—perhaps only a single dose after each meal or only at the time of distress but with no consistent attention to *acid control*.

The fundamental principle of the Sippy treatment is control of free hydrochloric acid in the stomach content throughout the day and the night. The measures used include the use of a nonirritant diet, high in protein because this means high in acid-combining value. For most patients milk and cream mixture will be found the most practical, convenient and palatable source of protein food. To meet special indications, gelatin, gelatin and cornstarch or cereal mixtures, cottage cheese or casein hydrolysates may be substituted but the principle remains the same. The larger the quantity at one feeding and the longer the interval between feedings, the higher will be the acid curve and the more antacid will be required to control the acidity. Frequent small feedings such as the original hourly schedule therefore have a technical advantage. For those patients who tolerate alkali poorly a half-hour feeding schedule may be used and this principle is carried to its limit in the continuous drip feeding of Winklestein. This method is readily available only in hospital and therefore in most instances only long enough to start treatment. It is available as a means of getting under control certain cases presenting unusual difficulty (e.g., excessive night secretion) but for most patients its advantages do not compensate for its added inconvenience.

For the past twenty-five years we have usually started patients with ulcer hemorrhage upon immediate feeding and an antacid schedule. This was initiated because so many patients admitted with hemorrhage have not previously been thoroughly examined but prove ultimately to have duodenal ulcer with varying degrees of obstruction, pyloric spasm and night secretion. Under these conditions the ulcer continues to be exposed to acid secretion during a fasting period and it was therefore deemed wise to start at once on a program designed to control acidity throughout the day and the night. This immediate institution of feeding accomplishes everything which can be expected from the Meulengracht regimen. Nothing is gained by the inclusion of coarse foods and a general diet which cannot be more readily accomplished by the immediate institution of a Sippy type regimen. If, at the outset of management, when the supplemental feedings included in the diet are limited to soft, bland foods, there is any question of vitamin deficiency, it is a simple matter to administer supplemental doses especially of vitamins B and C. As a rule the diet by the end of the first two or three weeks is sufficiently varied as to leave no question of any nutritional deficiency. The calorie intake may be readily adjusted to the patients requirements, increasing or decreasing the quantities and proportions of milk and cream to bring about either a gain or loss in weight if desirable.

The list of antacids available to supplement the protein of the diet in the control of acidity has been gradually increased over the years. Sodium bicarbonate, which was our principal reliance years ago, was

soon abandoned because of its tendency to disturb body acid-base equilibrium, and for the past twenty or twenty-five years has had little place in oral therapy. It may, however, be used mixed with milk in continuous drip feedings where the use of insoluble alkalis is not practicable. Colloidal suspensions of aluminum hydroxide may be similarly used and are less prone to precipitate alkalosis.

For the patient who is well adapted to the hourly regimen the alkalis most frequently used in this clinic are calcium carbonate, calcium phosphate, magnesium oxide and tribasic magnesium phosphate. Kirsner¹ has performed a service in pointing out the usefulness of the calcium compounds and their relative freedom from untoward effects. Many clinicians have lost sight of the fact that the high molecular weight of the phosphates gives them a relatively low acid-combining value per gram.² Aluminum hydroxide in colloidal suspension has a relatively high acid-combining value and little or no tendency to cause the development of alkalosis. Unfortunately the tablet forms are less effective and the liquid form involves the inconvenience of the weight of bottles and liquid. It is unfortunate also that there is at the present time no official preparation which is as satisfactory as the proprietaries. Mucin, which enjoyed a limited popularity for a time, is now little used because of its unpalatability and inconvenience. When used it is usually mixed with milk and chocolate or some other flavoring to cover its objectionable taste. It then becomes necessary to use a few doses of alkali at the end of the day's schedule to control acidity from the time of the last feeding to the end of the digestive period.

In any antacid regimen it is important that control aspirations be done at regular intervals and that the specimens be titrated for total acidity as well as tested for free acid. The acid-combining value of the protein in the diet is such as to make possible as much as 80 to 100 points of combined acid in aspirated specimens. Protection of the ulcer depends upon controlling *free* acid, but when the total or combined acidity is low it usually means that larger doses of alkali are being used than necessary and this is one of the factors in the etiology of alkalosis. Erroneous statements have frequently been made to the effect that alkali administration causes an increase in acid secretion. This may happen with sodium bicarbonate but with the antacids more commonly used it is not uncommon to find a marked decrease in secretion after a short period of treatment. To continue, therefore, with the original dose of alkali and without further tests is to unnecessarily invite alkalosis.

In any discussion of ulcer treatment at the present time it is appropriate to call attention to the value of *gastroscopy* as a diagnostic measure and as a means of helping to determine the progress upon any given course of therapy. It is probably our best means of recognizing early carcinoma in the stomach. In spite of the fact that we must

still reckon with a factor of error in our interpretation of the findings which it makes possible, it is an extremely valuable method of examination. It is to be hoped and expected that further progress in lens making and in lights and photographic equipment will make possible direct objective records of the findings and thus remove some of the human error in recording for comparison the findings in any series of examinations of a given patient over a period of time. Gastrosopic findings provide their maximum value when closely correlated with the clinical and roentgenological findings.

Neuropsychiatric Approach.—In the field of psychosomatic medicine much progress has been made in the recognition of the role played in the etiology of ulcer as exemplified by Cases II and III. The evidence does not warrant the assumption, however, that this is the only etiologic factor. Case IV, for example, presented no ulcer symptomatology until the patient was 53 years of age and there was at that time no evidence of psychic stress or trauma. Unfortunately it is easier to recognize these factors than to correct them. Many individuals temperamentally unsuited to extremes of nervous and emotional tension find themselves in occupations or domestic or social situations to which they are ill adapted. Some progress is being made in the neuropsychiatric approach to the problems of this category and the physician who has the confidence of his patient can in many cases get to the bottom of the problem more readily than the psychiatrist who has not the advantage of long previous contact with the patient and with other members of the family and business associates. There is undoubtedly a need for more neuropsychiatric training for the average physician and especially for the internist of the future. A great many ulcer patients may be benefited by prescribing rest and vacation periods, change in occupation and such changes in the mode of life of the patient as can be instituted to lessen the emotional stress.

Parenteral Therapy—The field of parenteral therapy was hailed a few years ago by the protagonists of histidine, synodal and the like as the answer to the ulcer problem, but time has proved the fallacy of these claims. While it is true that some of these substances were capable of giving temporary relief from ulcer pain or distress, carefully controlled series of cases showed little or no actual healing and there is in the literature ample evidence of serious complications developing while patients were undergoing therapy of this type. The brightest ray of hope from this type of therapy comes from the work of Ivy⁶ with enterogastrone and of Sandweiss⁷ with urogastrone. These substances, probably identical or closely related, have yielded excellent results in experimental animals and in a limited number of patients. The natural supply of these substances is so limited as to render them unavailable for other than experimental purposes at the present time. Future hope from this direction will probably depend upon analysis and the development of synthetic methods of production.

Surgical Approach.—In the field of surgical approach the outstanding contribution of recent years has been the work of Dragstedt² on vagotomy. His experimental studies have shown a marked reduction in volume and acidity of gastric secretion following complete vagus section. It is to be noted in many of the protocols submitted that free acidity has been reduced more than total acidity and this has not been entirely explained in the reported studies. One must remember that the total acidity is the best index of the amount of acid secreted and that free acid represents the total secretion minus the amount of acid which can combine with the available protein and mucus in the stomach contents. There has been adequate evidence of ulcer healing after vagus section and this has been repeatedly reported in patients with stoma ulcers following resection or gastroenterostomy and in patients with markedly excessive night secretion. The method has not yet been in use long enough to allow us to fully study the subsequent course of such patients or to evaluate other possible incidental effects of vagus section. Some of the physiological studies have suggested the possibility of undesirable side-effects on esophageal function, gastric and/or intestinal motility or secretion. Even though some undesirable effects may become evident, the value of this operation in facilitating the healing of previously intractable ulcer may prove to outweigh such disadvantages. Only time and further observation can provide the answers to these questions.

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ACUTE ENTERIC INFECTIONS

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RECENT surveys have indicated a higher incidence of enteric infections in this country than has been previously recognized. It is necessary, therefore, to maintain a constant alertness for the presence of such conditions as bacillary dysentery, amebic dysentery and food poisoning in the differential diagnosis of acute diarrheal diseases. The purpose of this paper is to review the important clinical features of these three enteric infections, and to outline the most effective methods of treatment.

BACILLARY DYSENTERY (SHIGELLOSIS, SHIGELLA COLITIS)

Bacillary dysentery is an infectious disease of the colon, and occasionally also of the ileum, caused by bacteria of the dysentery group. The dysentery bacilli comprise a large group of micro-organisms which are separated into various types by means of their cultural characteristics and serum reactions. The four main classifications are (1) *Shigella dysenteriae* Shiga-Kruse, (2) *Shigella Schmitz*, (3) *Shigella paradysenteriae* (Flexner, Hiss-Y-Strong) and (4) *Shigella sonnei*.

Bacillary dysentery occurs sporadically and epidemically in all parts of the world, wherever the habits of people are unsanitary. Its distribution, thus, is one of hygienic rather than geographic influence. According to Hardy and Watt, bacillary dysentery probably is the most important cause of endemic acute diarrhea in older children and adults in this country. The disease is transmitted by fecal contamination of water, food (especially uncooked fruits and vegetables) and cooking utensils. It is transmitted indirectly by the housefly.

The earliest anatomic lesion originates in the lymphoid follicles of the large intestine. These become infected and give rise to numerous shallow ulcerations. The mucosa is diffusely hyperemic, edematous and friable, and bleeds easily. The inflammation is especially severe in the rectum and sigmoid colon. A gangrenous inflammation of the entire mucous membrane has been described in the most severe cases.

Clinical Manifestations—The incubation period of bacillary dysentery ranges from twelve hours to seven days. The disease varies in severity from a mild, apparently harmless diarrhea to a toxic, fulminating, choleraic illness. In acute bacillary dysentery the symptoms begin suddenly with colicky pain in the abdomen, nausea, vomiting and

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diarrhea The stools are watery and contain blood, mucus and pus and there is usually an absence of fecal material. The number of stools per day may increase to twenty or thirty. Rectal tenesmus is marked. The temperature often rises to 39.4° or 40° C (102.9° or 104° F.), and may be intermittent or remittent. The loss of electrolytes and body water in the stools and vomitus is considerable and dehydration not infrequently develops. In some cases, the reduction in circulating blood volume may be so marked as to result in shock.

Physical examination reveals evidence of dehydration and toxemia. The abdomen is tender along the course of the colon. The sigmoidoscopic appearance of the bowel is that of a generalized inflammatory reaction. The entire mucosa is hyperemic, edematous and friable, and contains many small superficial ulcers. Sanguinopurulent material and excessive quantities of mucus are present within the lumen of the bowel.

Microscopically, the stools of bacillary dysentery are characterized by the presence of very large numbers of polymorphonuclear leukocytes. Red cells are numerous. In addition, a much larger cell, the endothelial macrophage, often is seen in the early stages of the disease. It may be round, oval or bilobed. Its cytoplasm contains vacuoles and granules of various kinds, and sometimes even ingested erythrocytes or leukocytes.

Diagnosis.—The clinical diagnosis of bacillary dysentery requires a constant awareness by the physician of its presence. In a sudden mass outbreak it is easily recognized. It should always be suspected in any group in which sporadic cases of diarrhea persistently appear. Accurate diagnosis depends upon the early isolation and identification of the causative organism. Culture of the blood-tinged mucus on SS agar or desoxycholate-citrate agar is the most effective means of recovering the dysentery organisms. Agglutination tests with the patient's serum have not proved sufficiently reliable to serve as a useful diagnostic aid.

Treatment.—The patient should be kept at complete bed rest. The usual precautions regarding isolation must be observed. The withholding of food is desirable during the first twenty-four hours. Liquids, such as rice or barley water, clear broths and tea may then be administered. These are preferably given warm and at frequent intervals. The diet is enlarged as the patient improves, to include eggs, toast, butter, custards, puddings, well-cooked cereals, mashed potatoes and chicken. Dietary restrictions should be maintained until all evidence of the disease has disappeared. The application of heat to the abdomen relieves the abdominal discomfort. Atropine sulfate, 0.001 gm., also may be helpful.

Dehydration is treated most effectively by the intravenous administration of isotonic sodium chloride solution, a sufficient quantity

should be given to ensure a urinary output of 1500 cc daily. There is no sound basis for the use of castor oil or colonic irrigations. Saline cathartics have been recommended by various clinicians but there is no unanimity of opinion regarding the necessity or benefit from this measure. The administration of bacteriophage has yielded indifferent results. Antidysentery serum probably is of value only in the Shiga type of dysentery. Penicillin has proved ineffective in this disease.

The value of sulfonamide therapy in the treatment of bacillary dysentery is now definitely established. Excellent results have been reported following the use both of absorbable compounds such as sulfathiazole and sulfadiazine, and less readily absorbed sulfonamides, such as sulfaguanidine and sulfasuxidine. Hardy and Watt have noted beneficial effects also with sulfamethazine, sulfamerazine, sulfapyrazine and sulfathalidine. Flexner varieties of *S. paradyenteriae* were most sensitive to these preparations and Sonne the least sensitive. Inasmuch as the dysentery bacilli grow on or in the bowel wall, the absorbed sulfonamides may have an added advantage in that these compounds approach the bacteria both from the tissues and the lumen of the bowel.

Sulfaguanidine may be given in an initial dose of 3.5 or 7 gm followed by 3.5 gm every four to six hours until three consecutive stool cultures are negative. Sulfadiazine may be administered in an initial dose of 2 or 4 gm, followed by 1 gm every four to six hours until the cultures are negative. The dosage recommended for sulfasuxidine is 0.25 gm. per kilogram of body weight initially, followed by 0.04 gm per kilogram of body weight every four hours for approximately six days. Five to seven days of chemotherapy are usually required in the majority of cases. Experience has shown that recovery is more rapid, the earlier in the disease sulfonamide therapy is instituted.

Illustrative Cases

CASE I—A 24 year old soldier, a member of a railway operations battalion, was admitted to the hospital with a history of nausea, vomiting, abdominal cramps and diarrhea which had developed suddenly ten days previously. Six to nine stools containing small amounts of gross blood were passed daily. Additional symptoms included chilly sensations, fever and general malaise. The patient stated that several others in the unit had become similarly ill at approximately the same time. Paregoric, bismuth and tincture of belladonna had been prescribed without relief of symptoms.

Physical examination revealed a moderately ill patient with evidence of dehydration. The temperature was 38.4° C. (101.1° F.). There was generalized abdominal tenderness. Sigmoidoscopy demonstrated a severe diffuse inflammation of the mucosa of the rectum and sigmoid with numerous small superficial ulcerations. A large amount of blood tinged fluid was present in the lumen.

The cultures of the bloody fluid and watery fecal evacuations were positive for *B. dysenteriae* Flexner. Three thousand cubic centimeters of 5 per cent glucose in isotonic saline were administered during the first twenty-four hours. Heat was applied to the abdomen and sulfaguanidine was administered in the dosage out-

lined above. The symptoms subsided promptly. The stool cultures became negative after seven days of chemotherapy and the patient was returned to duty in ten days.

CASE II—A 22 year old soldier, a member of the same unit, was admitted to the hospital on the same day with similar, but less marked, symptoms, of twelve days' duration. Symptomatic therapy, likewise, had proved ineffective. Physical examination revealed mild distention of the abdomen and slight tenderness over the colon. Sigmoidoscopy disclosed a mild inflammation of the mucosa of the rectum and sigmoid. Stool cultures were positive for the Flexner dysentery organism. The cultures became negative after five days of chemotherapy with sulfaguanidine. The patient's symptoms subsided completely and he was returned to duty in eight days.

CASE III—A 31 year old soldier, a member of the same unit, was admitted to the hospital five days later with a history that, seven days previously, he had become suddenly ill with nausea, abdominal discomfort and diarrhea. Five to six watery stools were passed, no gross blood was seen. The patient recovered after a period of thirty-six hours, and felt well until one day before admission. At this time he again became ill with abdominal cramps, watery stools, headache, fever, nausea and vomiting.

Physical examination disclosed an obviously sick and dehydrated patient. The temperature was 39.6° C (103.3° F). There was tenderness over the descending colon. Sigmoidoscopy revealed a moderately severe inflammation of the rectum and sigmoid with numerous small hemorrhages and a sanguinopurulent exudate in the lumen of the bowel. *Bacillus dysenteriae* Flexner was isolated from two stool cultures. Recovery was prompt after intravenous treatment with 5 per cent glucose in isotonic saline solution and the use of sulfaguanidine.

Five additional soldiers from this organization subsequently were hospitalized because of acute bacillary dysentery. Three of the group admitted having drunk water from unauthorized sources. Samples of this water, unfortunately, were not available for bacteriological study.

Comment—Although the clinical and epidemiological features in these patients were suggestive of bacillary dysentery, an interval of almost two weeks elapsed before this possibility was considered. These cases again emphasize the fact that examination of the stools for pathogenic organisms should be a routine procedure in all patients with diarrhea. The excellent response to the use of parenteral fluids and sulfaguanidine is in accord with many previous observations.

AMEBIC DYSENTERY

Amebic dysentery is a specific infectious disease, involving primarily the large bowel and the adjacent segment of the ileum, caused by *Endamoeba histolytica*. It is most prevalent in the tropics and subtropics, but occurs in all parts of the world. The incidence of amebiasis in this country has been variously estimated as from 5 to 20 per cent. The presence in the civilian population of individuals who have developed carrier states following amebic infections while in military service presumably will increase the prevalence of this disease. Amebic dysentery is transmitted (1) by the contamination of food or water

with fecal material containing the cystic forms, (2) by the use of human excrement in the fertilization of vegetable gardens, (3) by the droppings of flies and cockroaches and (4) by lower animals such as monkeys and rats. The principal sources of infection are so-called "carriers" or infected individuals who present no symptoms. Cysts may remain viable in feces for two weeks, and may persist in water for a month or more; they withstand freezing for one year.

When the cysts are swallowed, they pass through the stomach unimpaired. Excystation occurs in the mildly alkaline medium of the small bowel, and the small metacystic amebae escape to pass down to the region of the cecum. The amebic infection is essentially different from that of bacillary dysentery. Whereas the latter infection is relatively shallow, seldom extending below the superficial half of the mucosa which is infiltrated with myriads of neutrophils, the amebic infection involves the submucosa and occasionally the muscular layer, in addition to the mucosa. In the uncomplicated amebic lesion there is no appreciable infiltration of leukocytes. Trophozoites of *E. histolytica* are present in considerable number. The early lesions are found in the region of the cecum, including the appendix, distal segment of ileum, ileocecal valve and proximal portion of the ascending colon. The rectum and sigmoid colon is the next most frequently involved portion of the bowel.

Clinical Manifestations—It is often impossible to determine the natural incubation period in amebic dysentery because of the lack of accurate information as to just when infection occurred. In some individuals it is apparently only several days, while in others it extends over a period of weeks and even months. The severity of the disease is extremely variable. Many individuals infected with *E. histolytica* do not present symptoms. The onset may be abrupt, or preceded by a variable period of mild distress. In acute amebic dysentery the symptoms consist of an attack of colicky pain in the abdomen, followed by the passage of semifluid stools with blood and small amounts of mucus. These stools contain fecal material and are in contrast to the watery, nonfecal evacuations of blood, pus and excessive quantities of mucus characteristic of bacillary dysentery. Fifteen or twenty bowel movements may be passed daily. Rectal tenesmus usually is not marked. Chills or chilly sensations, malaise, headache, anorexia, nausea, vomiting and abdominal distention may occur. The temperature frequently is moderately elevated. Physical examination usually reveals no significant abnormalities except for abdominal spasm, and tenderness over the involved portion of the bowel.

The leukocyte count may be normal or moderately increased. The duration of an attack without treatment, varies from a few days to several weeks. The severity and duration apparently depend upon the extent of involvement of the intestine, the resistance of the patient to

infection and the presence or absence of serious secondary bacterial infection

Sigmoidoscopy in the typical case reveals discrete ulcers located usually on the prominent folds of the intestinal wall or on the valves of Houston. The ulcers may be as small as 2 to 3 mm in diameter or as large as 2 to 3 cm, the usual size is 3 to 8 mm. The margins are undermined, irregular and overhanging. There is generally a surrounding zone of hyperemia. The base of the ulcer may contain a grayish-white accumulation of material, composed largely of numbers of *E. histolytica*. The mucosa between the ulcers is so mildly inflamed as to seem relatively uninvolved. In some cases the inflammation is diffuse and severe and the typical ulcerations cannot be identified. In many individuals with active diarrhea due to *E. histolytica*, the mucosa of the rectum and sigmoid appears normal or only mildly hyperemic.

Diagnosis.—The diagnosis of amebic dysentery should be considered in any patient whenever the previously described symptoms are encountered. The final diagnosis is based upon the careful warm-stage microscopic examination of fecal smears suspended in salt and iodine solutions. The trophozoites are present in the watery evacuations whereas the formed stools contain only the cysts. The collections of blood-tinged mucus and the exudate obtained directly from rectal lesions at proctoscopy constitute the best material for the demonstration of amebae. The use of the zinc sulfate centrifugal flotation technique, which separates the cysts and floats them on the surface, increases the likelihood of accurate diagnosis. A diagnosis should not be accepted as negative in suspicious cases until at least three to six stool examinations have revealed no parasites.

Treatment.—Patients with acute amebic dysentery should be maintained at complete bed rest. A liquid diet with clear broths, gruel and tea may be given initially. The diet during convalescence should be bland and low residue in type. The use of supplementary vitamins has been recommended. In general, laxatives and cathartics are contraindicated and may be harmful. Drugs such as bismuth or opiates, used to control the diarrhea, may interfere with specific chemotherapy and should rarely be necessary. Penicillin and sulfonamides are ineffectual as specific therapy, but are useful adjuncts in the treatment of cases complicated by secondary bacterial infection.

No single compound can be relied upon to cure all cases of amebic dysentery or amebiasis. It is necessary, therefore, to employ a combination of drugs. The most useful of these are emetine hydrochloride, chiniofon (yatren), carbarsone, diodoquin and vioform.

Emetine hydrochloride in nontoxic amounts is a relatively ineffective amebicide. Its greatest value consists in the treatment of such a complication as amebic hepatitis or abscess of the liver. Under ordinary conditions, it is probably indicated chiefly for the control of severe

diarrhea It is given preferably by subcutaneous injection in doses for adults not to exceed 0.03 gm ($\frac{1}{2}$ grain) twice a day, or 0.06 gm (1 grain) once a day during the period of diarrhea, but not for more than six or eight days Patients should be confined to bed while receiving emetine and for several days thereafter Repeated electrocardiograms are desirable for the early detection of myocardial damage Emetine therapy should not be repeated until at least six weeks have elapsed Its use is unnecessary in asymptomatic or mild cases unless the endamebae prove resistant to other drugs and inadvisable in patients with heart disease The toxic effects include nausea, vomiting, muscular weakness, neuritis and myocarditis The drug should be discontinued immediately if any toxic signs appear Emetine bismuth iodide has been recommended It is given as a loose powder in gelatin capsules in doses of 3 grains nightly for twelve consecutive nights This compound may produce toxic effects similar to those of emetine hydrochloride and, therefore, must be used with caution

Chiniofon or carbarsone may be administered concurrently with emetine hydrochloride Chiniofon is one of the most effective of the amebacidal compounds It is a synthetic drug containing approximately 28 per cent iodine Each tablet contains 0.25 gm and is enteric-coated The dose for an adult is 0.75 to 1 gm (11 to 15 grains) three times daily by mouth for seven or eight days It may also be administered in the form of a retention enema of 200 cc. of a 2 per cent warm water solution daily The rectal tube should be inserted carefully and the solution introduced without pressure Not infrequently, a profuse diarrhea develops during the use of chiniofon, however, the diarrhea per se is not a contraindication to continued therapy

Carbarsone is a valuable amebacidal drug which contains approximately 28 per cent arsenic It is given by mouth in doses of 0.25 gm ($3\frac{3}{4}$ grains) twice daily for seven to ten days Toxic symptoms are rare, but abdominal distress, with nausea, vomiting and diarrhea, may appear, very rarely, exfoliative dermatitis and visual disturbances occur Carbarsone is contraindicated in the presence of hepatic disease

Iodoquin, containing 61 per cent iodine has proved useful in the author's experience Each tablet contains 0.21 gm It is given by mouth in doses of 0.63 gm (96 grains) three times daily for seven to ten days No significant toxic symptoms have been reported Vioform contains from 39 to 40 per cent iodine, and is administered by mouth in doses of 0.25 gm ($3\frac{3}{4}$ grains) three times daily for ten days All these courses of treatment with iodine or arsenic-containing preparations may be repeated, if necessary after an interval of ten to fourteen days without therapy

The prognosis for complete recovery in the average uncomplicated case is good, if specific antiamoebic therapy is instituted immediately The results of treatment should be checked by repeated clinical and

laboratory studies. A patient should not be released from medical supervision until three stool examinations are negative for *E. histolytica*. Subsequently, the stools should be examined once a month for at least three months

Illustrative Cases

CASE IV—A 24 year old Negro soldier was admitted to the hospital with a diagnosis of "internal hemorrhoids." He had experienced abdominal cramping pain and diarrhea, with the passage of semiliquid stools containing blood and "pus," for a period of two years. One year previously, the patient had been subjected to a hemorrhoidectomy elsewhere without relief of symptoms. The stools apparently had not been examined, nor had a sigmoidoscopy been performed. The patient became progressively worse in the four months preceding admission, with gripping abdominal pain, diarrhea, occasional bouts of chilly sensations and fever, and anorexia, nausea and nervousness. As many as fifteen loose stools, containing gross blood, were passed daily. There had been a weight loss of approximately 15 pounds.

Physical examination revealed an acutely ill man, moving about restlessly in bed. The temperature was moderately elevated. There was marked spasm and tenderness over the entire abdomen. Sigmoidoscopy disclosed a severe, diffuse inflammation of the rectum and sigmoid with numerous moderately large ulcerations. The findings were not typical for an amebic infection, but examination of material taken directly from the lesions revealed the presence of trophozoites of *E. histolytica*. Therapy included the usual supportive measures. Emetine and carbarsone were given concurrently in the doses outlined above and were followed by a course of diodoquin. The symptoms and the inflammation of the rectum and sigmoid subsided rapidly. However, cysts of *E. histolytica* persisted in the stools. The patient subsequently was evacuated from the hospital and a more complete follow-up period was not possible.

CASE V—A 13 year old boy was admitted to the hospital because of a persistent diarrhea of two years' duration. In August 1944, while fishing, he had taken a drink of water from a brook which was thought to contain spring water, the "brook" actually proved to be a sewer outlet. Between two and three weeks later, he suddenly developed diarrhea with eight or nine watery stools per day. After one week, the stools contained mucus and gross blood. The diarrhea had continued to the time of admission. The patient also complained of malaise and pain in the left lower quadrant of the abdomen and the suprapubic region after each bowel movement. There was no fever, nausea or vomiting. Three physicians had been consulted and diagnoses of "colitis" and "infectious diarrhea" had been made. Various forms of therapy, including sulfonamides, had been used with only temporary improvement. Roentgen studies of the chest and gastrointestinal tract, made elsewhere, had been normal. The stools apparently had not been examined for parasites or pathogenic organisms.

Physical examination revealed a slightly undernourished and underdeveloped boy, there were no other significant findings. Sigmoidoscopy revealed numerous bleeding ulcerations of varying size, one typical lesion was approximately 3 to 4 mm in diameter, surmounted by a grayish-white material and surrounded by a zone of hyperemia. The intervening mucosa appeared to be only mildly inflamed. Warm-stage examination of the material from this ulcer disclosed the characteristic trophozoites of *E. histolytica*.

The patient's symptoms were promptly relieved following the administration of small doses of emetine and diodoquin.

Comment—Cases IV and V illustrate the importance of careful examinations of the stools and sigmoidoscopy in the diagnosis of amebic dysentery. The infection in both instances had persisted unrecognized for two years because of the omission of these procedures. Case V is of particular interest in that a definite incubation period of between two and three weeks can be established for the development of symptoms.

FOOD POISONING

Food poisoning is an acute gastroenteritis produced by the ingestion of food which is contaminated with bacteria, bacterial products or with poisons of chemical, vegetable or animal origin. The most important types of food poisoning are those caused by the staphylococcus and salmonella organisms.

Staphylococcus Food Poisoning—Staphylococcus food poisoning probably is the most common type of food poisoning at the present time. The illness is produced by an enterotoxin elaborated by the staphylococcus and present in the food before it is eaten. Many varieties of food have been implicated, a partial list includes cheese, chicken gravy, milk, custard pie, cream-filled eclairs and tarts, chocolate eclairs, tongue sandwiches, ham and liver sausage. Custard-filled bakery goods, ham and tongue probably have been responsible for the greatest number of outbreaks.

Clinical Manifestations—The symptoms appear within one to six hours, usually three hours, after the ingestion of the contaminated food. The incubation period is influenced by the amount of enterotoxin consumed and the susceptibility of the patient. The onset is sudden, with salivation, followed promptly by vomiting, retching, abdominal cramps and diarrhea. The severity of the attack varies. In mild cases there may be nausea and vomiting without diarrhea, or cramping abdominal pain and diarrhea without vomiting. Headache, muscular cramps and sweating may occur. In severe cases, blood and mucus may be observed in the stools and vomitus. Dehydration frequently develops as a result of the marked loss of body water and electrolytes in the vomitus and stools. The dehydration and diminution of circulating blood volume may be so severe as to produce a state of shock, with prostration, subnormal temperature and a marked drop in the blood pressure. It is characteristic for symptoms to develop almost simultaneously, though with varying severity, in a group of individuals who have ingested a contaminated food.

Recovery usually is prompt and occurs in from one to five days, it may be prolonged in some cases for one to two weeks.

Treatment—There is no specific drug or serum therapy available for the treatment of staphylococcus food poisoning. If the patient is vomiting all food and liquid should be withheld for six to twelve hours or more, depending upon the persistence of symptoms. After this period,

water may be administered in small amounts, gradually increasing the quantity until it is well tolerated. Soft foods are added subsequently. The patient should be maintained on a bland diet for several days after the attack. Dehydration is treated by the intravenous administration of isotonic saline and 5 per cent glucose solutions, 3000 to 4000 cc. may be necessary during the initial twenty-four hours. Blood plasma also should be given if shock has supervened. The course of the blood pressure is a useful clinical indicator of the quantity of fluid which a patient may require. It is unnecessary to empty the stomach by tube or to administer cathartics, since most of the offending food has been eliminated in the vomitus and stools.

The prevention of staphylococcus food poisoning, as well as other types, depends upon the proper storage, refrigeration and handling of food. Kitchens and bakeries should be required to maintain superior standards of sanitation. Food handlers should be inspected frequently and regularly; those found to harbor infections of the skin or respiratory tract must not be allowed to handle food.

Illustrative Case—The following case illustrates the typical clinical features of severe staphylococcus food poisoning and the prompt recovery following treatment.

CASE VI—A 33 year old soldier was admitted to the hospital at 6:30 P.M. He stated that at 9:00 A.M. of the same day, he and four other soldiers had eaten a meal which included turkey left over from the supper of the previous evening. At 10:30 A.M. he suddenly became ill with intense nausea and vomiting, severe abdominal cramps, diarrhea and chilly sensations. These symptoms continued unabated and soon were associated with marked weakness and a sensation of "blackening out." The other four men had fallen ill at the same time, but their symptoms were less marked.

Physical examination revealed a critically ill male, in shock. The temperature was subnormal, the pulse rapid and weak, the heart tones faint. The blood pressure was 76 mm. of mercury systolic and 62 mm. diastolic. There was a mild but definite cyanosis of the lips, ears and nail beds. The abdomen was soft but diffusely tender. The erythrocyte count was 5,61 million, hemoglobin 90 per cent, the leukocyte count was 21,300 with 92 per cent polymorphonuclears and 8 per cent lymphocytes. Two thousand cubic centimeters of isotonic saline solution and 500 cc. of plasma were administered intravenously over a period of twelve hours. The blood pressure and pulse returned to normal, and in twenty-four hours all symptoms had subsided. Fourteen hours after admission the erythrocyte count measured 5,09 millions, the leukocyte count 12,050 with 78 per cent polymorphonuclear cells and 22 per cent lymphocytes. The patient was returned to duty three days after admission.

Salmonella Food Poisoning.—*Salmonella* is a generic name applied to a group of bacteria known also as paratyphoid organisms. More than 100 types of salmonella have been implicated as etiologic agents in acute gastroenteritis. The two principal species are *S. aertrycke* (also known as *S. typhimurium*) and *S. enteritidis*, other common types are *S. choleraesuis* and *S. Panama*. Salmonella food poisoning is an infection, toxins or toxic substances play no role. Outbreaks

of salmonella food poisoning have been described following the ingestion of such foods as improperly cooked meat, raw milk, custards and puddings. Animals and birds probably constitute the main reservoir for human infection.

Clinical Manifestations—According to Dack, one of the most characteristic features of the disease is the time required for symptoms to develop after the ingestion of the organisms. A period of at least seven or eight hours elapses before symptoms develop in the most susceptible individuals, twelve to twenty-four hours elapse in the majority of cases, and twenty-four to thirty hours or longer may elapse in a few cases. The onset of symptoms may be abrupt, with chills, headache, cramping abdominal pain, nausea, vomiting and diarrhea. The stools are foul smelling and soon become watery. Prostration, muscular weakness, faintness and thirst may occur. There is almost always a rise in temperature. The severity of the disease differs in different outbreaks and among various individuals in the same outbreak. Ordinarily, it subsides within several days to one week. Salmonella food poisoning should be suspected whenever the symptoms noted above appear simultaneously among individuals who have partaken of the same food.

Accurate diagnosis depends primarily upon the recovery of the organisms from the feces and/or the ingested food. Unfortunately, this is not often possible.

Treatment—The treatment is the same as that recommended for staphylococcus food poisoning. Sulfaguanidine and sulfasuxidine exert a strong bacteriostatic effect on *S. choleraesuis*. Most varieties of salmonella, however, do not respond to sulfonamide therapy.

Streptococcus Food Poisoning—Outbreaks of food poisoning due to the alpha type streptococcus have been reported much less frequently than those due to the staphylococcus or salmonella organisms. Symptoms usually appear in five to eighteen hours after ingestion of the contaminated food. The clinical manifestations and the treatment are the same as in the preceding types of food poisoning.

Epidemic Diarrhea, Nausea and Vomiting—This is not a true food poisoning but sometimes may be confused with it. The chief difference is the apparent spread of the disease by contact. Pupils in a schoolroom, for example, may be affected as a group when no common source of food supply has been evident, and cases do not develop simultaneously as is the rule in food poisoning. The cause is not known but it is thought that the infection may be due to an air-borne virus which gains entrance through the respiratory or gastrointestinal tracts. The onset is sudden. There is practically no rise in the temperature or pulse rate and the symptoms subside in one or two days. The condition usually is so mild that no treatment is necessary. Rest in bed and the local application of heat relieve the abdominal dis-

comfort. Abstinence from food usually controls the nausea. Parenteral fluids are rarely necessary.

CONCLUSIONS

1. The clinical manifestations and treatment of acute bacillary dysentery, amebic dysentery and food poisoning have been reviewed.
2. The presence of these diseases should be suspected in all patients with symptoms of an acute enteric infection.
3. Careful examination of the stools for pathogenic organisms and *Endamoeba histolytica*, and sigmoidoscopy should be performed in all patients with acute enteric infections.

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STEATORRHEA

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INTRODUCTION

STEATORRHEA, an intestinal phase of faulty fat metabolism, is often a source of great diagnostic and therapeutic confusion. The multiplicity of generic factors and the frequent resemblance to infectious diarrhea, functional bowel disorders and other intestinal disturbances make it a subject of considerable interest, while the prolonged or recurrent debility resulting from its presence, together with the fact that this condition frequently fails to be considered in the diagnosis of diarrhea, emphasize the practical need for a better understanding of the problem.

Definition and Classification of Steatorrhea—Steatorrhea may be defined as an increase either in the total amount of fecal fat above the normal of 10 to 20 gm per day or in the percentage by weight of fat in the dry stool, the upper normal limit being about 20 per cent. For the purposes of this discussion, steatorrhea may be classified etiologically as follows: (1) *pancreatic disease*—inflammation, calculi, neoplasm, cyst, (2) *"idiopathic" steatorrhea*—tropical and nontropical sprue, celiac disease, (3) *miscellaneous*—obstruction of mesenteric lymphatics as by neoplasm, lymphoma, tuberculosis, trauma, intestinal lipodystrophy and lipogranuloma, gastrojejunocolic fistula, regional enteritis, sequels of protozoan and bacillary dysenteries.

The average daily wet weight of the feces of normal individuals is about 150 gm with a total fat content of approximately 15 gm. In contrast, the fecal weight in a series of thirteen cases of steatorrhea¹ averaged 743 gm with an average fat content of 45.1 gm per day.

The normal composition of the fecal fats is given by Fowweather² as follows:

	Mean	Variation
Dry matter, per cent	21.1	4.6-38.0
Total fat, per cent of dry weight	17.5	7.3-27.0
Neutral fat, per cent of dry weight	7.8	2.5-11.8
Free fatty acid, per cent of dry weight	5.0	1.05-10.0
Soap, per cent of dry weight	4.6	.54-11.4

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It is commonly assumed that an increase in the percentage of neutral fat and a decrease in fatty acids signifies incomplete fat digestion as a result of pancreatic disease, whereas an increase in total fat, the percentage of fatty acids being normal or high, is taken to mean that fat digestion is normal but absorption is poor, a condition exemplified by sprue. While there is some ground for these statements, recent evidence obtained both from patients and experimental animals indicates that figures for the percentage composition of the fecal fats should be employed with caution in the differential diagnosis of steatorrhea.^{3, 4}

The effects of steatorrhea upon the organism as a whole may be profound. An intestinal content rich in fat is in itself conducive to diarrhea which, as part of a vicious circle, further interferes with fat absorption. The excretion of from 50 to 70 gm. of fat daily in the feces represents a loss of from 450 to 630 calories or nearly one fourth of the energy requirements of the body. When large amounts of fatty acid are present in the intestinal contents, as in sprue, their propensity for combining with calcium to form soaps which are then excreted results in a calcium deficiency which may be expressed as osteoporosis and, in some cases, frank tetany. Moreover, the absorption of the fat-soluble vitamins is seriously impaired so that attempts to correct the loss of calcium by the oral administration of vitamin D and related compounds are only partially successful. As might be expected, night blindness as a result of vitamin A deficiency is common. Other defects traceable to faulty digestion and absorption of important nutrients are anemia, hypoproteinemia and edema, the last two symptoms being especially prominent in the steatorrheas which are accompanied by failure of protein digestion such as diseases of the pancreas.

PANCREATIC STEATORRHEA

Steatorrhea Associated with Pancreatic Calculi, Pancreatic Cyst and Chronic Pancreatitis.—Patient C. H., a white man, aged 58, was hospitalized with complaints of abdominal pain, diarrhea and weight loss.

Thirty years prior to admission he had first noted vague severe upper abdominal distress. Exploratory laparotomy at that time had revealed a large pancreatic cyst from which 3 liters of fluid were evacuated with uneventful recovery. During the following ten years, he had noted bouts of colic, nausea and vomiting of two to three days' duration three to four times each year. At a second laparotomy a gastro-enterostomy had been performed with partial relief of the vomiting but the colicky upper abdominal pain persisted. Two years before hospital admission, he had suffered an acute attack of severe abdominal cramps lasting four days and accompanied by some 12 large frothy stools daily. He had experienced two similar attacks in the next eight months. The volume and frequency of the bowel movements gradually increased and at the time of admission he was having 8 to 10 large foamy stools daily.

Physical examination revealed an emaciated man about 60 years of age. Widely distributed intestinal peristalsis was visible through a thin abdominal wall. The remainder of the examination was not remarkable.

X-ray studies showed nonvisualization of the gallbladder, a well functioning

gastroenterostomy in an otherwise normal stomach and duodenum, and a normal colon. There was a branching mass of small calcification in the right abdomen, near midline (Fig 14), which seemed in the stereoscopic films to be in the region of the pancreas. Routine blood and urine studies were normal except the leukocyte count which ranged between 10,000 and 13,000. Other laboratory findings were not significant with the possible exception of a low serum amylase. Both the oral and the intravenous glucose tolerance test gave mild diabetic types of curves. Gross examination of the stools showed them to be soft, pale yellow in color, voluminous, acid to litmus and containing food particles. The sudan III stain showed excess fat. The stool fat content was markedly increased (41.2 per cent of the dry weight) and on one occasion the serum calcium and phosphorous were reduced.



Fig 14 —Calcification is apparent in the abdomen.

On operation Dr. A. Brunswick extirpated a markedly thickened and inflamed gallbladder filled with large stones. The anterior surface of the pancreas was adherent to the transverse mesocolon. A longitudinal incision over the upper left anterior aspect of the head of the pancreas disclosed a dilated pancreatic duct (4 mm. in diameter) containing numerous concretions varying from bean to millet seed in size. After these were removed exploration revealed the ducts to be patent throughout. The patient made a satisfactory recovery and suffered no recurrence of the colicky pain. However, he continued to have 1 to 3 formed stools daily. The diet was maintained at about 350 gm. of carbohydrate, 125 gm. of protein and 100 gm. of fat and the patient received tincture of belladonna 20 drops three times daily, and a multiple vitamin preparation. He was discharged 119 days after admission and seventy-one days postoperatively.

Differential Diagnosis.—The most important laboratory aid in the diagnosis of pancreatic lithiasis is the demonstration by x-ray of densities in the region of the gland (Fig. 14). These are easily overlooked in routine gastrointestinal studies, being obscured by the overlying barium, and films of the gallbladder area often fail to extend sufficiently far toward the left. A so-called "flat plate" of the abdomen should be ordered in every suspected case. Failure to find the characteristic shadows does not necessarily exclude the diagnosis, for many of the concretions removed at operation are too small to be seen on the x-ray film. The association of chronic pancreatitis and atrophy of glandular tissue with the development of steatorrhea and diabetes has been reported in long-standing pancreatic calculi and is well demonstrated in this case. Similar findings were noted in two others with pancreatic lithiasis. The oral and intravenous glucose tolerance curves in all three were moderately diabetic in type. It is by no means always so, but a normal or diabetic curve is good evidence that one is not dealing with active sprue. Plasma proteins tend to be lower than in sprue, whereas hypocalcemia is more marked in the latter disease, but these differences are not sufficiently uniform to be relied upon. The serum amylase is of no value in the diagnosis of chronic disease of the pancreas.

Treatment.—Surgical exploration is usually indicated in suspected pancreatic lithiasis as removal of the calcareous deposits is the treatment of choice. The fact that in some 30 per cent of cases of pancreatic lithiasis there is an associated cholelithiasis serves to emphasize the difficulty of distinguishing between these two conditions. The average mortality of pancreaticolithotomy is 10 per cent.⁵ While colic may be relieved and further damage to the gland be avoided by operation, steatorrhea may not improve and diabetes which is already present is but little affected.

A low fat diet is often of considerable value. It tends to relieve diarrhea by diminishing the amount of irritating fatty acids and soaps in the bowel and decreases the high excretion of calcium and fat-soluble vitamins.

Some observers have found pancreatic steatorrhea to respond favorably to the administration of massive doses (10 to 30 gm daily) of pancreatic extract, but others have noted little or no improvement in the condition with this therapy.

"IDIOPATHIC" STEATORRHEA (SPRUE)

Patient P S, a white woman, aged 21, was admitted to Billings Hospital complaining of intermittent diarrhea, anorexia, fatigue and loss of weight of two years' duration. She had always resided in the Middle West. On several occasions she had been told that she had anemia for which liver and iron were prescribed with indifferent success. Two years before admission, she had eaten a great deal of raw fruit, following which she had experienced diarrhea marked by numerous large, loose,

yellow, sour-smelling stools without blood. Over the next two years, similar attacks had occurred on the average of once every four months. These lasted about two weeks and were always preceded by marked fatigue and vertigo. During one episode soreness of the tongue had been noted. A weight loss of 15 pounds had occurred during the two year period.

Physical examination revealed nothing of significance except moderate under-nutrition. The red blood count was 4.2 to 4.4 million per cu. mm. and the hemoglobin 54 to 58 per cent of normal. Detailed blood studies showed a normocytic, hypochromic anemia. Other routine laboratory studies were normal. The stools were voluminous and mushy and at times frothy with a sour milk odor and occasionally a metallic sheen. Microscopic examination showed an excess of fat globules which stained with sudan III. No parasites or ova were found in repeated examinations and the benzidine test for occult blood was negative. Cultures revealed no unusual flora. Agglutination tests of the serum with the typhoid-dysentery group were within normal limits. Free hydrochloric acid was present in the gastric secretion. The oral glucose tolerance test gave a flat curve with values as follows: fasting 82, one-half hour, 91, one hour, 88, two hours 91 mg per 100 cc. In contrast, the intravenous glucose tolerance test gave normal results.

The patient was intensively studied in the hospital during a period of thirteen months. X rays of the gastrointestinal tract, at first reported normal, were later found to show segmentation and pooling of barium in the small bowel with distortion of the mucosal pattern such as has been described in vitamin deficiencies and sprue. A satisfactory remission of symptoms and gain in weight took place on a low fat, high carbohydrate diet (approximately 500 gm of carbohydrate, 100 gm. of protein and 50 gm. of fat). In a determination of the patients' tolerance for fat, it was found that when the daily dietary fat was 100 gm. she experienced slight nausea and anorexia. When the daily dietary fat was increased to 200 gm., the nausea and vomiting were severe. Symptoms and fecal fat declined sharply when the fat intake was reduced below 100 gm., but when this was again increased, nausea reappeared at a level of 100 gm. Treatment was then started with injections of 3 cc. of crude liver extract (Lederle) three times weekly, purified vitamins of the B complex* and 15 gm. of brewers yeast per day. The patient regained her appetite and was free of symptoms even with a fat intake of 200 gm. per day, though the stools now contained 43 per cent of the dry weight, or 12 gm. of fat each day. Symptoms were again induced with an intake of 250 gm. despite medication.

These studies bring out (1) the beneficial effect of a low fat diet, (2) the gradual increase in fecal fat with increments of fat intake, (3) the sharp rise in fat excretion when the limit of tolerance was reached, and (4) the effect of crude liver extract and B vitamins in enabling the patient to consume amounts of fat which without such medication she could not tolerate.

This patient has been seen at irregular intervals to date. She continues to adhere to a relatively low fat diet and takes from 2 to 3 cc. of crude liver extract once or twice per week in addition to a "shot-gun" vitamin preparation and ferrous sulfate daily. She is generally in good health and rarely has a loose bowel movement. The blood count remains at a low normal level.

Differential Diagnosis—This syndrome is characterized by a history of long-continued diarrhea with copious, often frothy, and some

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times frankly oily stools, loss of weight, sore tongue, flatulence, weakness, anorexia and, oddly enough, at times polyphagia. Tetany is not rare. Physical findings include pallor, malnutrition, abdominal distention, glossitis and sometimes edema. Thus, except for the absence of pain, the clinical picture does not differ strikingly from that seen in other forms of steatorrhea. The diagnosis is to a considerable degree one of exclusion, and one in which the aid of the laboratory is required. While fecal weight and grams of fecal fat were somewhat greater in pancreatic steatorrhea than in the idiopathic form, differences are not large and there is much overlapping in individual instances. Moreover, the averages for fecal nitrogen in the two groups were almost identical. Patients in both groups may have achlorhydria, anemia, hypocalcemia, hypoproteinemia and impairment of fat absorption. By far the most valuable laboratory procedure, in our experience, is the oral glucose tolerance test. The curve is almost uniformly flat in the active stage of sprue and normal or diabetic in steatorrhea of pancreatic origin.

The response to treatment is also of aid in the diagnosis of "idiopathic" steatorrhea. Improvement with adequate doses of crude liver extract (the concentrates are not so effective) favors the diagnosis while failure of improvement militates against, though does not exclude it. The disease must be distinguished from pernicious anemia, with which it has many features in common including, in some instances, diarrhea. In pernicious anemia the excretion of fat is not excessive and the glucose tolerance curve is often of the diabetic type. In sprue, the anemia is frequently not macrocytic and hyperchromic, free hydrochloric acid may be found in the stomach and combined cord degeneration does not occur.

Treatment.—The size and frequency of the doses of liver extract required in sprue are greater than in pernicious anemia. From 2 to 6 cc. once to thrice weekly may be necessary to induce a remission and the maintenance requirement may be as high as 2 cc. every one to two weeks. Because the nature of the specific deficiency has been unknown, it has been customary to supplement the extract with brewers' yeast 6 to 12 gm. daily and multiple vitamin preparations. In view of recent reports indicating the effectiveness of crystalline folic acid (*Lactobacillus casei* factor), it seems possible that the identity of the specific substances may have been discovered and that the treatment of this syndrome may become much simplified. Folic acid in doses of 15 mg. daily (intramuscularly) for eighteen days has been stated to produce striking remission of anemia, diarrhea and glossitis and a reversion of the glucose tolerance curve from flat to normal, although it seems to have but little effect on the impaired absorption of fat.⁸ Spies and associates⁹ report the successful treatment of tropical sprue with folic acid. These investigators noted the clinical response with an oral daily

dose of 10 mg. of the preparation to be as satisfactory as were amounts of up to 200 mg daily given by the same route Folic acid has also been used with encouraging results in other forms of macrocytic anemia, including pernicious anemia, thus lending point to the old question of whether Addisonian anemia and sprue may not be closely related

The low fat diet constitutes one of the most important features of treatment. It follows that the carbohydrate and protein must be high in order to supply the necessary calories with which to combat under-nutrition. One of our patients, by consuming liberal amounts of soft drinks in addition to the more usual foods, was able to raise the carbohydrate of her diet to more than 600 gm daily without discomfort

STEATORRHEA DUE TO MISCELLANEOUS CAUSES

Space permits only brief mention of three cases in which the following diagnoses were made (1) cirrhosis and regional enteritis (service of Dr George Dick, autopsy), (2) lymphoblastoma involving the mesenteric lymph nodes (service of Dr Walter L. Palmer, operation) and (3) transient diarrhea of unknown origin in a patient with diabetes In the first of these cases the diagnosis of sprue had been originally entertained but later abandoned because of normal glucose tolerance curves and failure to respond to liver extract. Pancreatic disease was then suspected although no calculi were discernible in the x-ray films At operation the pancreas was found to be grossly normal and a biopsy specimen proved to be normal microscopically There was incipient cirrhosis of the liver but no other abnormal findings were noted. After operation the excess fat gradually disappeared from the stools, but the patient continued to have diarrhea, anorexia and vomiting, became psychotic and died in extreme cachexia some three years after the onset of illness At autopsy extensive, chronic, inflammatory changes of a nonspecific nature suggestive of regional enteritis were found in the small bowel

In the second case the presence of rather severe abdominal pain which accompanied the patient's steatorrhea had led to the tentative diagnosis of pancreatic neoplasm It is of interest that the serum amylase was greatly increased, values ranging from 463 to 644 units. The glucose tolerance curve was normal on one occasion and flat on another One determination of pancreatic ferments after duodenal intubation gave normal results while a subsequent test showed practically no activity At exploratory operation, no surgical disease was found and biopsies of the pancreas and liver were reported as normal The patient was discharged with a provisional diagnosis of sprue. Eight months later he was readmitted with severe epigastric distress and vomiting X ray examination of the gastrointestinal tract, previously normal now showed stiffening and narrowing of the second por

tion of the duodenum. At a second operation a large mass of enlarged lymph nodes was found within the mesentery of the jejunum and ileum which on microscopic examination proved to be lymphoblastoma. The patient died four months later in another institution, where permission for autopsy was not obtained.

SUMMARY

1. Any chronic or intermittent diarrhea characterized by large, frothy stools with a "sour-milk" odor suggests steatorrhea. The suspicion can be strengthened by direct microscopic examination of the feces and confirmed by quantitative determination.

2. In fixing etiology, the first step is a search for pathogenic organisms in the stools, since excessive fat excretion may accompany or follow infectious diarrhea of bacterial or parasitic origin.

3. The next step is a careful roentgenologic study of the gastrointestinal tract, *including a plain film of the abdomen* designed to show pancreatic stones. If they can be demonstrated, the diagnosis is established at once.

4. If no calculi are found, the steatorrhea may still be due to (a) other pancreatic disease (obstruction of the duct by radiolucent material, cyst, tumor or inflammation), (b) disease of the intestines, mesentery or lymph nodes, or (c) "idiopathic" causes (sprue).

5. If the glucose tolerance curve is not flat, that is, if it is normal or diabetic, and if there is no response to treatment with adequate amounts of crude liver extract (and folic acid?) a condition other than "idiopathic" steatorrhea is likely and surgical exploration may be indicated, with attention not only to the pancreas but also to the intestine itself.

6. Certain laboratory findings are common to most cases of steatorrhea, whatever the cause, and thus are of little help in differential diagnosis. These include anemia, hypoproteinemia, hypocalcemia and impairment of fat absorption. Likewise, determinations of gastric acidity, serum amylase, pancreatic enzymes in the duodenal contents, fecal nitrogen, and the partition of the fecal fat between neutral fat, fatty acids and soaps have, in our experience, been of no aid in distinguishing one type of steatorrhea from another.

7. A low fat diet is of proven value in the treatment of the steatorrheas.

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NEPHRITIS AND NEPHROSIS

WILLIAM A THOMAS, M D °

THE purpose of this discussion is not so much to bring out the most recent concepts and advances in the study of nephritis and allied conditions, as to sketch the manner in which these conclusions have been reached, and particularly to emphasize the fact, either forgotten or ignored, though fully accepted, that the clinical picture of a patient in any of the various stages of this disease is in most respects totally unlike the entity resulting from partial or complete absence of renal activity. For many years following Bright, indeed until recently, it was believed and taught that the various manifestations of this malady could be directly attributed to one or another aspect of renal excretory insufficiency, and progress in developing our present concepts of the disease has consisted largely in a process of pilfering from the kidneys and delegating those functions to other systems, usually with permanent success, although occasionally such a transfer, apparently valid, must be reversed, much to the confusion of its advocates, as will be emphasized later.

Specifically, in analyzing the varied manifestations of nephritis, it has been customary to designate them as due to disturbances of renal, vascular or tissue aggregates, with a progressive increase of those falling under the latter two headings at the expense of the renal group. Edema was probably the first to successfully and permanently abandon the renal shelter and to be placed under the tissue heading, granted that serum protein is a tissue and that electrolytes qualify as essential in the activity of protoplasm. It is surprising to note how recently, certainly not more than three decades ago, edema was generally presumed to result from inability of the kidneys to excrete water. About that time one heard whispers of "tissue thirst," or "electrolytic balance," and there slowly developed the realization that edema and anuria were not primarily renal failure, and that practically any kidney, regardless of the degree of damage, could excrete water, though it might be only water, containing no solids, if water were available or set free by the tissues. McClure and Aldrich, with their skin absorption test, gave great impetus to this concept, encouraging confidence in the new point of view and stimulating further investigation of the novel and attractive theory, all leading to our present valid concepts of water balance, diuresis and edema.

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All such raids on renal territory have not been so permanently successful, however. In the case of *hypertension*, the major role of the kidneys, theretofore accepted, was questioned by Gull and Sutton as early as 1872, when they demonstrated a diffuse arteriocapillary fibrosis involving the entire vascular bed and emphasized the nonrenal aspect of the condition, while later Albutt proclaimed that such organic disease of arteries was in many cases not demonstrable or was insufficient to cause the elevation of blood pressure or the increased peripheral resistance. He believed that there was a generalized vasoconstriction of unknown origin, leading finally to organic changes in the small vessels, and that the kidney was not necessarily involved. This concept was generally accepted, and hypertension, in its simplest classification, was composed of two main groups, (1) *nephritic* or *renal hypertension*, with clear evidence of renal origin, due to nephritis, obstruction of urinary passages, cystic kidneys, and periarteritis nodosa, in which the individual would presumably die from uremia, and (2) a *nonrenal* group in which marked elevation of blood pressure might persist for many years without evidence of renal impairment, the patient succumbing to congestive heart failure or a vascular disaster. There remained a third classification, nonrenal and not important in this context, comprised of basophilic adenomas of the pituitary and other brain tumors, adrenal tumors, hyperthyroidism, menopausal and psychic hypertension, possibly toxemias of pregnancy, and coarctation of the aorta.

It was with the second of the main groups, the nonrenal hypertension, that many were particularly concerned. It came to be known as *essential hypertension*, and for many years was universally considered as an entity unrelated to any renal function. The project of pilfering had been complete and successful, with a large group of hypertensives taken from the renal category and firmly established as a vascular disorder, when along came Goldblatt, showing that renal ischemia of varying degrees can in experimental animals duplicate the precious nonrenal hypertension, and a very large proportion of such cases were promptly returned to the renal fold.

Thus, while the renal role in the clinical course of nephritics has been greatly depleted, a few of the important phenomena remain. To return to the original thesis, what are the symptoms of uncomplicated absence of renal function? This can be illustrated by unilateral nephrectomy in dogs. Such animals do not in any manner resemble a human nephritic or a dog made nephritic artificially. These nephrectomized dogs die in the course of ten to fourteen days, with a picture of progressive asthenia. There is no elevation of blood pressure, no coma in most instances, no convulsions, no edema despite unrestricted food and fluid, and in so far as one can judge, no headache.

In earlier days preceding general pyelography before nephrectomy,

there were occasional instances in which, following removal of a diseased kidney, it was found that no functioning kidney remained. Study of such cases revealed a course precisely similar to that in nephrectomized dogs, in that the patient experienced progressive weakness and fatigue, anorexia without nausea, no increase of blood pressure, little or no edema and no headache, coma or convulsions, in spite of extreme azotemia and acidosis. Death was quiet and appeared to result from extreme weariness, in contrast to the uremic ending. From these facts, as well as extensive confirmatory evidence, it would appear that azotemia as such is not responsible for symptoms in nephritis. The following case history serves as an example.

Some years ago there entered Presbyterian Hospital a 50 year old woman whose only symptom was fatigue—actually exhaustion. It became apparent that she had an almost total lack of kidney function, as no phenosulphonphthalein was excreted, urea clearance was below 5 per cent, urea nitrogen 110 mg, nonprotein nitrogen almost 500 mg per 100 cc. and carbon dioxide combining power 22, without ketosis. A retrograde pyelogram revealed that both kidney regions consisted of numerous closely packed stones, and at autopsy it was found that both kidneys consisted of very thin cortical shells, each surrounding a mass of alkaline salt stones which had obliterated all trace of pelvis, calyces, and normal markings thus presenting a condition of pure renal insufficiency, similar to those previously described. Her skin was parched and dry with no edema, she was mentally sluggish but clear, and had no headache, twitching, or convulsions. Respiration was deep and sighing but regular. She presented a condition in striking contrast to nephritics, who, with definitely less azotemia, have headaches, convulsions and coma.

NEPHRITIS

Nephritis is a generalized systemic disease, involving many or all actively functioning tissues of the body, and all too often, concerned with the state of the kidneys, and concentrating all efforts to improve or restore their function, other organs or metabolic imbalances are neglected. In acute hemorrhagic nephritis, the most common cause of death is cardiac, with rapid rise in blood pressure, excessive heart load, pulmonary edema and death from heart failure. This fact is very generally recognized by pediatricians, who encounter the condition frequently, while it is not uncommon to see, in the case of an adult, the physician so concerned with the renal aspect of the disease that, even with increasing peripheral and pulmonary edema, the cardiac aspect is ignored while he redoubles his efforts to promote diuresis by a renal procedure. In this respect, nephritis resembles rheumatic fever, in which attention is so frequently focused on the cardiac aspect, or on the joints, that the infectious nature of the condition, anemia, malnutrition and other equally vital considerations are forgotten.

In nephritic patients, therefore, both in study and treatment of patients, and in teaching, each individual symptom and sign should be critically considered, with the purpose of determining to which role it should be credited, renal, vascular or tissue. By so doing, the physi-

cian achieves a deeper understanding of the patient and of the disease, following which he may more successfully and intelligently attack the individual, varied and frequently confusing problems as they are presented.

Diagnostic Procedures—Confronted with the problems of a nephritic patient, the physician is required to answer many specific questions, and to issue definite directions regarding his future activities and medical program. In order to do so accurately, there must be a basic plan of study in each case, which should include simple blood chemistry and serum proteins, and one or more tests of renal function which may be phenolsulphonphthalein, urea or other clearance tests, some modification of the Mosenthal test showing ability to concentrate and dilute (concentration is a function of tubules and dilution a function of glomeruli), electrocardiogram, chest plate, complete blood and urine analyses, and when feasible, an intravenous pyelogram with the second film taken in the erect position, to reveal any undue ptosis or possible unilateral renal disease. In the presence of hypertension, standard sedation and nitrite tests to determine the vascular lability, and the cold pressor test for hyperactivity, are indicated. With all this done, there remains one examination whose value, when properly conducted, may equal or exceed that obtained from all other tests—inspection of the eyegrounds. This is a procedure that will not be of great value when done by the average well trained internist, or for that matter, by many ophthalmologists. However, the information obtained from study of the fundus by one experienced in such work gives information of inestimable value. After detailed study of the entire length of the four main vessels in each eye, the interpretation follows: "This is the picture of essential benign hypertension of short duration or intermittent in character"—"Moderately advanced stage of malignant hypertension"—"This is not a toxemia of pregnancy, but a case of essential hypertension of long duration which has become pregnant." Unfortunately such talent is not generally available, and lacking such assistance, it is well to train oneself in the use of the ophthalmoscope and attempt to correlate the data obtained by other means with the eyeground findings.

Management—With such information in his possession, the physician can proceed to instruct the patient, confident that the examination has so impressed him that he may break down old traditions. This is particularly true with respect to *protein*, especially of animal origin. Even today many patients come to the office, hospital or clinic firmly indoctrinated with the belief that they may eat no meat—in fact a substantial proportion of them are suffering more from protein deprivation than from the original malady. This belief is held by patient, family and frequently by the family doctor himself—all must be converted and convinced—which can be accomplished more readily

if there has been a careful study than if not. Nevertheless, every relapse or unfavorable turn in the course of hypertension or nephritis—and there are certain to be many—will be attributed to the meat ordered by the doctor.

NEPHROSIS

In any gathering of physicians interested in renal problems there sooner or later arises the question of nephrosis. Is there a clinical entity of lipoid nephrosis, or is it merely the nephrotic syndrome of nephritis? There are sound, able men of both persuasions, and it is rare to see one converted from one camp to the other. True enough, there are borderline cases that neither side will claim, either because they resemble nephritis too greatly, or because they are not pure nephrotic, but there seem to be cases sufficiently distinct to be classified either as lipoid nephrosis or as nephritis, and presumably the same patient has been demonstrated as each.

Clinical Features.—Although in the minority, it might be interesting to advocate the case of lipoid nephrosis, since there are several features of the condition which are distinct from those commonly seen in nephritis, and since it is always instructive to engage in an honest argument. The disease is encountered in childhood and youth, usually in males, and without a preceding history of specific infection, such as scarlet fever, tonsillitis or rheumatic fever. The clinical findings are very definite and usually all are present, consisting of generalized edema, frequently massive with accumulation of 50, 70 or more pounds of fluid, proteinuria, at times in large quantities—30 gm or more in twenty-four hours, with absence of red blood cells and leukocytes and no increase in casts by Addis count, no elevation of blood pressure, no retention of nitrogenous products in the blood, lowered serum protein with reversal of albumin-globulin ratio, and great elevation of cholesterol and esters in the blood. This is sufficiently distinct from ordinary nephritis to warrant the assumption that it is a distinct entity, but there is one additional feature that is particularly difficult to discount. These patients die, or more exactly, did so before the advent of sulfonamides, almost universally of one cause, a pneumococcal infection, practically always peritonitis. This in itself sets the disease apart from nephritis, since that particular fate is so unusual in the latter that it is not recognized as a complication.

Another point of difference is that the onset of nephrosis is preceded, not by infection as in nephritis, but by *chilling*, and careful questioning with this in mind will in almost every case bring out such a forerunner. It may be swimming in cold water on a hot day, driving with the automobile window open, dancing on a warm evening and cooling in a breeze, going from a hot kitchen to stand on the porch—becoming chilled in a duck blind, chilling from getting wet followed by exposure

to wind, working in the refrigerator room of a butcher or packing plant, and numerous similar causes of chilling

Disturbances of Protein Metabolism—The fundamental mechanism of nephrosis is well understood although various minor phases remain obscure. Primarily there is a loss of serum protein through the kidneys. Debatable is the reason for this—whether it is renal damage, with increased permeability of the glomerular capillaries, or due to such modification of the serum proteins that they are no longer retained in the vascular bed and behave as would a foreign protein. This possibility will be considered at greater length. Furthermore, if the process is one of capillary damage with increased permeability of glomerular vessels, is it not probable that this process is not limited to the kidney, but that similar damage and increased permeability may be present throughout the entire capillary bed, with loss of serum protein into the interstitial fluids, thus reducing the gradient of colloidal osmotic pressure between blood and extravascular fluids, thereby promoting edema?

Regardless of this problem, the loss of serum protein with the consequent reduction of colloid osmotic pressure provides an ample basis for the edema. Since the albumin fraction of the proteins is relatively small in comparison with the large globulin molecule, albumin is lost at a greater rate than globulin due to its smaller size, and colloidal osmotic pressure reduced in a disproportionate degree, since a gram of albumin contains many more molecules than a gram of globulin and therefore exerts a correspondingly greater osmotic pressure, these facts also explaining the reversal of the albumin globulin ratio.

There is adequate evidence to consider lipoid nephrosis a disturbance of metabolism, particularly of proteins, and a satisfactory explanation of the marked elevation of cholesterol has not been advanced. Thyroid deficiency was presumed to be a cause at one time and, although these patients exhibit no signs of such lack and are found to have normal basal metabolic rates, both when taken between active episodes and when making due allowance for water retention, nevertheless they may tolerate enormous doses of thyroid—as much as 16 or 24 grains of an active preparation daily for a period of several months without any signs of excessive medication—and without benefit to their condition.

Regarding the possible failure in protein metabolism, the following facts must be considered. The various fractions of serum protein are highly specific immunologically, both from species to species and in the same species. Thus euglobulin precipitated by 25 per cent saturation with ammonium sulfate, pseudoglobulin at 45 per cent saturation and albumin at 100 per cent, are all immunologically specific and as antigens can produce precipitins in dilutions up to one part in a million each one specific for its own fraction and inactive toward

other fractions of the same blood. Naturally these fractions are also species specific, so that each animal or human has within his circulation proteins which cannot be distinguished from one another by a chemist or a physicist, but belong only to that species by immunological standards. Furthermore, the kidneys, and presumably the entire capillary bed, dispose promptly of any protein in the blood which does not completely conform to its individual specifications. Thus a foreign protein, whether it be egg albumin, whole blood or a fraction thereof, injected intravenously, is excreted by the kidneys, frequently so little altered that it retains its special characteristics. This being so, it would appear that, with respect to larger protein aggregates, there are present in the blood only those proteins which conform to the particular pattern of that person, and that all other proteins are eliminated.

At the upper end of the protein scale, the relatively enormous molecules of albumin, globulin and albumoses are antigenically specific, while at the lower end, amino acids and peptone are nonantigenic. They may be injected or absorbed by other routes repeatedly without producing antibodies and without resulting reactions. Somewhere at the polypeptid level or above, this specific property begins and becomes increasingly specific in the ascending scale.

Is it not possible that this disorder known as lipoid nephrosis is a failure on the part of the body to completely and accurately synthesize from the amino acids derived from assimilated protein, the specific higher protein structures characteristic to that body? Obviously, the variations between albumin molecules, for example, are very small, since chemical and physical methods fail to distinguish between albumin from different species, and a slight error in configuration of the final product would designate it as a foreign protein, marked for excretion. If such is not the case, it is extremely difficult to explain a type of damage to glomerular capillaries which allows the escape of molecules of the magnitude of serum proteins, and manages to retain the very small electrolytes, urea and similar aggregates.

Increased Capillary Fragility.—That there is a factor of increased permeability of glomerular capillaries in nephrosis, in addition to the hypothetical disorder of protein metabolism, is indicated by some preliminary results from work in progress. Szent-Gyorgyi, working in Hungary before the recent war, isolated from the rinds of citrus fruits a substance which he believed reduced permeability of blood vessels, especially capillaries and, believing it to be a vitamin acting in much the same manner as ascorbic acid, named it vitamin P—for permeability. A similar or identical substance has been obtained from pomegranate, tobacco, and recently in large amounts from buckwheat, and has been available for clinical investigation. Griffith and Lindauer¹

demonstrated that the effect of this preparation (Rutin—supplied by Abbott Laboratories) was not on permeability, but on capillary fragility, as shown by Göthlin's test (tourniquet or blood pressure cuff modification of Rumpel-Leeds test) They further showed (1) that in a large group of hypertensives, those with increased fragility as evidenced by a high fragility index suffered ten times the frequency of retinal and cerebral hemorrhages as those of corresponding hypertensive levels with normal fragility, (2) that administration of Rutin restored abnormal to normal fragility with corresponding decrease in frequency of hemorrhages, and (3) that when Rutin was discontinued, increased fragility and frequency of vascular accidents recurred

Rutin Therapy—With these facts in mind, four cases of massive proteinuria were studied—two of the patients being definitely chronic nephritics, the other two as pure nephrotics as could be obtained Quantitative twenty-four hour urinary protein determinations were made on two successive days, Rutin therapy established for ten days, followed by two additional protein determinations Of the four patients only one of the nephrotics reacted with increased fragility, which responded promptly to Rutin therapy, with a decrease from 54 and 48 gm of urinary protein before treatment, to 12 and 9 gm on two successive days following Rutin. The other three who had normal fragility at the onset had no decrease in urinary protein following therapy The limited supply of Rutin at present precludes more extensive investigation, and conclusions cannot be drawn from a single, small series of cases It suggests however, that fragility and permeability may possess some properties in common, that those cases of nephrosis characterized by increased permeability may be distinguished by the fragility test from those in whom the major defect is possibly in protein synthesis, and that the former may be to some degree improved by alteration of permeability, possibly by some substance which at the same time corrects increased fragility

REFERENCE

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HYPERTENSION: THE HOPEFUL ASPECTS IN THE CLINICAL STORY

ITALO F VOLINI, M D , F A C P *

THE experimental and clinical contributions to the subject of hypertension present an extensive mass of material, much of which, in the application to the specific individual under survey, unfortunately produces considerable confusion and doubt in the mind of the practicing physician. As a finding obtained by an instrument, this evidence of high arterial pressure, taken alone, assumes in many instances too much importance to both patient and physician. In so far as the discovery of the elevated pressure stimulates the investigation of the organic and functional integrity of the various organs and systems of the body, including the complete study of the individual, it is a decided benefit, but when this discovery arouses the fears of the patient, even creating many and unrelated symptoms, it is a distinct detriment. The evil effects are aggravated if the dire possibilities are stressed or even mentioned by the physician. The hopeful aspects of essential hypertension must be given equal if not greater emphasis than the pessimistic patterns that can be painted by pointing to the localization of severe arteriolar disease in essential organs.

ESSENTIAL HYPERTENSION

Miss M S , an unmarried, retired school teacher, now 80 years of age, first came under observation in 1940 with a complaint of high blood pressure, "skipping of the heart" and palpitation. Hypertension was known to exist since 1920. There was a history of thyroidectomy in 1929. The blood pressure was 190/100. Definite tortuosity and periarterial streaking of the retinal arterial vessels were seen. Sclerosis and tortuosity were palpable in the peripheral arterial vessels. The heart was enlarged, measuring 11 cm. to the left of the midsternal line. Frequent ventricular premature contractions were found. There was no evidence of congestive heart failure. The 2-meter x-ray film of the chest revealed the left heart enlargement and some calcified areas in the aorta. The electrocardiogram showed left axis deviation with ventricular premature contractions. The physical examination and the laboratory studies revealed nothing otherwise particularly significant except pronounced varicosities of the veins of the both legs. The patient walks from three to five miles daily, usually in all types of weather conditions.

The patient's main complaint focalized upon the heart "skip." She was given a prescription for capsules as follows:

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R	Phenobarbital		300
	Quinidine Sulfate	4	000
	Quinine Hydrobromide	4	000
	Theobromine Calcium Salicylate	6	000
	Mix and divide into 30 capsules		

Sig. Take a capsule after breakfast and upon retiring

Upon her return visits much improvement was noted in the diminution of the frequency of the premature contractions. The arterial pressure remained the same. The capsules were continued, but were to be taken only at bedtime. In the course of one year she did not mention the extrasystoles, but became depressed and pessimistic over the elevated blood pressure.

Despite the attempted encouragement and reassurance that having lived with her blood pressure for at least twenty-one years without trouble, she could continue to enjoy the fruits of her mature years, her apprehension persisted. Something must be done. The capsule was changed as follows:

R	Phenobarbital		300
	Quinidine Sulfate	4	000
	Erythryl Tetranitrate		180
	Acetophenetidin	9	000
	Mix and divide into 30 capsules		

Sig. Take one three times a day

With this therapy there was a slight continued decrease in pressure which averaged 160 mm of mercury systolic and 100 mm diastolic. The medication was continued for several months upon reduced dosages. Headaches appeared which were considered to be the result of the medication. The patient felt much better, as a result of the reassurance and the knowledge that there was available a medicine that would lower her blood pressure when it might be necessary. All medication was discontinued. Upon the last examination in June, 1946, before she departed for her summer vacation at Chautauqua, the blood pressure was 200/100. She carried with her her 80 years and the physical ability to continue her long walks. There has been no medication for the past two years and no attempt to alter the routine of her existence. There are hopeful features in essential hypertension.

The symptoms of essential hypertension per se are in reality practically negligible. The subjective manifestations and the objective findings are produced by the vascular disease in its specific localization. The symptomatology is not the hypertension, which is merely a clinical sign obtained by an instrument. The clinical symptomatology is the result of, or is rather, arteriolar disease with its consequent effects and accidents. The clinical patterns produced depend upon the severity, the localization and the rate of evolution of the arteriolar damage. When the severity is great and the rate of evolution rapid the malignant phase of essential hypertension is indicated. Despite the fact the gravest indications of major localization in this phase are in the kidneys, extensive distribution of the arteriolar damage is evidenced by the profound changes frequently found in the ophthalmoscopic examinations and the episodes of intracranial symptomatology. The life history of the disease is short and progressive.

C S, aged 54, a salesman, was first seen October 1, 1945, with complaints of failing vision, headache, vomiting, shortness of breath at night, and a history of three "spells" of unconsciousness. Frequency of urine at night was pronounced. The weight loss of 30 pounds in the last three months was not of dietary origin. His complaints had been initiated by convulsion four months previously although he knew he had high blood pressure for the past four years. He believed he had been seriously ill for the past nine months. The examination showed many areas of hemorrhage in both eyegrounds with silver streaking, perivascular exudate and "cotton-wool patches." This evidence, encountered in the routine regional investigation, the first step in the physical examination, definitely indicated arteriolar necrosis. It explained his convulsions or spells and indicated the gravest outlook. The blood pressure was 220/150. The heart was enlarged, 13.5 cm. from the mid-sternal line. Gallop rhythm was present. The liver margin was palpable 2 finger-breadths below the costal margin. The deep tendon reflexes were excessively exaggerated although abnormality was not found. The specific gravity of the urine was 1.008, and albumin and casts were present. The electrocardiogram revealed left axis deviation with left ventricular strain and coronary insufficiency. The patient was ordered to the hospital. The renal functional examination indicated severe renal insufficiency with concentration diuresis studies showing fixation, creatinine above 10 mg. per 100 cc. and nonprotein nitrogen 153 mg. per 100 cc. The patient succumbed in twenty-three days despite obvious improvement in the heart symptomatology and findings.

This patient presented serious evidence in the ophthalmoscopic examination, in the heart, kidneys and brain. While the term "hypertensive" is used to describe this evidence—as hypertensive neuroretinopathy, hypertensive heart disease, hypertensive encephalopathy and the like—the arteriolar damage and not the degree of blood pressure deviation is the responsible mechanism.

The "benign phase" of essential hypertension is a term frequently employed to denote the phase of apparent well-being of a hypertensive individual. It is also called the red hypertension of Volhard. The ruddiness of the individual is associated with functional kidney integrity, "renal arteriolosclerosis without renal insufficiency." Despite the "benignity" of the condition, there is no assurance that the next moment may not bring an acute coronary episode, apoplexy, or the onset of left ventricular failure. On the other hand, the benign phase may be characterized, as clinical experience well attests, by a long period of years of comparatively good health. Even cerebral and cardiac episodes may be followed by many years of comparative comfort despite continued hypertension.

Mrs. V. N., when first seen on August 12, 1936, at the age of 61, gave a history of continuous high blood pressure since 1921. She was a highly tensioned individual, with extreme emotional irritability. Frequent readings showed the pressure to be 200 mm. of mercury systolic and 110 mm. diastolic. She was overweight. The eyegrounds revealed tortuous sclerotic vessels. The left heart border was 13 cm. to the left of the midsternal line. There was an apical systolic murmur and a systolic murmur over the aortic area. She had definite angina of effort. The urine and the kidney function were normal. She had continued as an office patient at intervals of one to three months. For many years she has been on control by sedatives of various

types, alone and combined with vasodilators. The rationale of this therapy will be discussed later. Significant variability could be produced in her hypertension, but the average high level continued. On several occasions readings such as 240 mm of mercury systolic and 130 mm diastolic were obtained. On May 16 1946 a reading of 190/100 was obtained.

Now at 71 years of age this patient's hypertension is apparently of about the same degree as at its onset in 1921 and at the beginning of treatment in 1936. The tempo of her life has been changed, her reactions altered, her emotional problems not completely but somewhat resolved. One certainly can apply the term "benign phase of essential hypertension" to this condition, which has through its benignity over the years permitted life and a measure of happiness to this patient.

The benign phase can be seen even in patients who have been close to death as a result of serious episodes of hypertension. The organic vascular lesions, once developed, are not reversible. Outside of the kidneys, however, focal rather than total episodes characterize the acute accidents. Under these circumstances healing by scar, by collateral circulation or even a *restitutio ad integrum* can be accomplished.

Mr. A. D. was first seen December 3, 1935 at the age of 53 for an acute anterior myocardial infarction due to coronary occlusion. Hypertension had been detected several years previously. He continued to direct a large manufacturing business until struck down by the coronary attack. He was seriously ill with considerable difficulty for about one year. The pressure dropped precipitously during the attack. From a level of 188 mm. of mercury systolic and 110 mm. diastolic on April 17 1936 the record shows 142/92, gradually rising at the end of 1936 to 190/110. Fluctuations with levels to 160/100 were produced by sedatives, iodides and vasodilators. Anginal pains continued. The physical activity was strictly limited because of the ease with which cardiac pain was produced. A recurrent attack of infarction occurred in August 1941 while the pressure which just prior to this episode was 188/110 dropped to 160/100. Recovery was slow, but sufficient for a winter journey to Florida where much improvement was produced. In April 1942 a severe collapse followed another attack. The pressure during convalescence in August 1942 was 130/80 but gradually rose to 170/94 by November 17, 1942. The patient could walk but a few feet when the pain would appear despite the taking of nitroglycerin. Gradual improvement has occurred, however so that now with a pressure of 180/100 he can walk about one block and with rest can proceed. Eleven years after a severe acute anterior myocardial infarction with preceding hypertension and several recurrences he, at 64 years of age, still possesses a benign hypertension.

The case of S. L., aged 56 years illustrates the course of hypertension with acute cerebral accident. At the age of 46 he was told he had a high blood pressure. In February 1941 he was seen in consultation for an acute right hemiplegia at which time his blood pressure was 230 mm. mercury systolic and 130 mm. diastolic. Convalescence and recovery were very slow. He was able to appear at the office in October 1942, when his pressure was still the same. The eyegrounds showed pronounced sclerosis. The heart was enlarged 12 cm. to the left of the midsternal line. The urine showed a marked trace of albumin with a specific gravity of 1.022. Complete neurologic restoration had occurred with exaggerated deep tendon reflexes remaining. The electrocardiogram indicated left axis deviation. Tests of renal func-

tion and intravenous pyelography were reported normal. Repeated serologic tests were negative. The patient has been seen at monthly or bimonthly intervals. He has been active, taking several business trips across the country, although he remains up but a few hours a day. Drug therapy has not made the slightest impression upon the arterial tension. Almost every drug and combination advised for hypertension has been used in treatment with no effect. The last examination in July 1946 revealed a pressure of 220 mm of mercury systolic and 140 mm diastolic. While a transition from the benign to the malignant phase is suggested, at this writing the symptomatology and signs of beginning renal insufficiency are not complete.

SECONDARY HYPERTENSION

The cases so far described have illustrated essential hypertension. All have been characterized by abnormally high systolic and diastolic pressures. If considered alone this sign will lead to possible serious diagnostic error and occasionally to actual harm to the patient. As in all medicine, thorough investigation is a necessity. A careful history, a complete physical examination which should include ophthalmoscopic examination of the retinal vessels, and neurological investigation comprise the first phase of the search for a possible etiologic factor in the hypertension. Laboratory studies should include blood study and urinalysis, functional tests of the kidney, intravenous and if necessary retrograde pyelography, chest films for heart changes, and electrocardiograms. By such a thorough study of the patient we can determine at least clinically whether the hypertension is associated with disease or structural change. If the latter is found the condition is secondary hypertension, as contrasted with primary or essential hypertension, the etiology of which is unknown and the diagnosis of which is an exclusion deduction, based on the absence of disorders which are known to result in hypertension.

Thus in organic arterial lesions and cardiovascular disease, hypertension accompanies aortic regurgitation, arteriovenous aneurysm, periarteritis nodosa, complete heart block and coarctation of the aorta.

J. H., a white youth aged 17 years, was referred after several examiners had discovered hypertension, with a diagnosis of high blood pressure or essential hypertension. His sister, a nurse, requested that something be done for this pressure elevation. He had no particular complaints, except that he noticed some slight dyspnea on violent exertion, appreciable for the past six or seven years. He was working as a clerk during the summer vacation, and attending high school during the school year. Measles at 3 years of age, diphtheria at 4 and a tonsillectomy at 8 constituted the only significant past complaints. There had been no history of rheumatic infection, growing pains, chorea or severe attacks of tonsillitis. The patient was of more than average intelligence, had an excellent body build and was very active physically.

The physical examination revealed a blood pressure reading of 190 mm of mercury systolic and 100 mm diastolic. The heart was slightly enlarged measuring 10 cm to the left of the midsternal line with the apex in the fifth intercostal space. There was a loud systolic murmur at the apex. A systolic murmur was audible over the aortic cartilage and was transmitted into the carotids. On the left side at the

lower margin of the eighth and ninth ribs, just below the angle of the scapula prominent pulsating vessels were noticed, throbbing and pushing out the skin with each pulsation. They were visible for a distance of about 2 cm. Likewise, in the interscapular area on both sides on a level with the transverse spines of the scapulae were pulsating vessels which coursed diagonally downward for about 5 cm., disappearing underneath the scapulae.

Of course the diagnosis was immediately suggested by these findings and blood pressure determinations made on the right arm showed a level of 198 mm. of mercury systolic and 100 mm. diastolic. The femoral pulse was barely appreciable, but no blood pressure reading could be obtained on either lower extremity. The dorsalis pedis pulse could not be obtained on either foot.

Temperature readings in the mouth were normal. The 6-foot film of the chest revealed the heart with slight enlargement to the left and extensive scalloping of the lower margins of the third to the ninth ribs inclusive. The scalloping was marked particularly on the left eighth and ninth ribs, where the pulsating intercostals were noted on the physical examination. This excavation of bone was not accompanied by thickening or new bone formation. In the flat plate there was an absence of the aortic knob. In the left oblique film the aortic arch was poorly visualized and terminated abruptly at the isthmus. The retroaortic and retrocardiac spaces were clear.

The electrocardiographic tracing revealed the tendency to right axis deviation with a prominent T in Lead I. In fact T_1 and T_4 were equal to the respective R waves. Further study showed normal circulation time by decholin, normal venous pressure and normal vital capacity. Coarctation of the aorta was responsible for the hypertension.

Various diseases of the endocrine system may be etiologic in the production of elevated arterial tension. The thyroid, the pituitary, the male and female gonads and the adrenals may be associated with or produce hypertension. Cortical or medullary tumors of the adrenal or chromaffin tissue outside of the suprarenals may induce the elevation. The cortical lesions probably produce their effects by excessive hormone formation of the desoxycorticosterone type. Hypertension can be induced by excessive amounts of this synthetic hormone introduced into the body.

M. P., aged 43, a barber, first came under observation July 5, 1939. His history was of a long tuberculous pulmonary involvement for which he spent several years in a tuberculosis sanatorium. The disease was believed to be arrested and he was discharged and pursued his occupation for about eight years. A year ago he noticed weakness which has grown progressively worse, with a weight loss of 35 pounds and a tired feeling so that he remained in bed most of the time. His friends called attention to the pigmentation which has gradually extended to his entire body.

On examination the blood pressure was 90 mm. of mercury systolic and 68 mm. diastolic, pulse 124, respiration 28, weight 102 pounds. The chest revealed extensive scarring from arrested tuberculosis of the lungs. The weakness was extreme. The pigmentation was diffuse, extensive and severe. Blood serum sodium and potassium were 209 mg. and 36 mg. per 100 cc. respectively. The pressure dropped to 78/50 before treatment was instituted. Basal metabolism was a -7. The specific gravity of the urine ranged from 1.022 to 1.005 and showed numerous pus cells. The complete record is a voluminous one and the present writing does not concern itself with the Addison's disease. The patient was treated by alternating irregular injections of synthetic desoxycorticosterone acetate and adrenal cortical extract. Some

improvement was obtained although the pressure did not exceed 102/70. On September 30, 1940, the calculation indicated a daily maintenance requirement of 75 mg desoxycorticosterone acetate. Thirteen pellets totaling 21 gm were at this time implanted subcutaneously through an open operative incision. The patient vomited and could not take fluids. Subsequently he went into a convulsion. His blood sugar was 49 mg per 100 cc. He recovered after glucose injections and his blood pressure immediately was 130/80. He improved rapidly but also his blood pressure rose precipitously despite cessation of extra sodium intake. The highest level reached was 198/120 on May 1, 1941. A note on the chart of this date states "a case of Addison's disease. He has had desoxycorticosterone implanted in his back and now has hypertension." The pellets gradually diminished in size. With their disappearance the patient showed a gradual reduction in blood pressure until he left the Cook County Hospital on June 21, 1942, when it was 140/90. The obvious mechanism was excessive hormone activity.

Again, various intracranial lesions may induce increased arterial tension. The most probable mechanism is intracranial pressure increase with interference with the blood supply to the vasomotor center. Tumors, injuries and hydrocephalus are most commonly found.

Hypervolemia from great liquid ingestion and polycythemia vera are credited with the production of hypertension.

Renal diseases of either medical or surgical character increase arterial blood pressure. Indeed, some investigators and clinicians credit the kidney with the responsibility for the production of essential hypertension. An elevated pressure is common and may be a major presenting symptom in glomerulonephritis, amyloid disease, pyelitis, pyelonephritis, hydronephrosis, congenital polycystic kidneys, ectopic kidney, lower genitourinary disease and obstruction to urinary flow. From the time of Richard Bright and later Tigerstedt and Bergmann, the kidney has been associated with the conception of hypertension. Where a surgical lesion of the kidney can be demonstrated as producing hypertension, other factors being favorable, the surgical attack should not be delayed.

THEORIES OF CAUSATION OF ESSENTIAL HYPERTENSION

Uncertainty and controversy still surround the causation of essential hypertension. The pathogenesis definitely suggests vasoconstriction of the arterioles, probably of the entire body but possibly focal—the splanchnic vessels, the kidneys, the vasomotor center—alone or combined. The initial and early stages are reversible, termed "labile," whereas the prolonged effects are medial wall hypertrophy, hemorrhages into the vascular wall and arteriosclerotic degeneration. These are irreversible or "stable." The rate of evolution is extremely variable. It may be very slow and gradual or rapid, fulminating and disastrous as found in the malignant phase of essential hypertension.

If the experimental work in dogs could be applied to the human, then the conception of the humoral etiology, most probably of renal origin, might be considered valid in essential hypertension. All hyper-

tension thus is renal hypertension. Renin, a normal constituent of renal tissue (a protein-like enzyme) acts upon hypertensinogen, a pseudoglobulin of the blood plasma, to produce hypertensin, the vaso pressor substance which causes pronounced vasoconstriction. *Antrenin* and *hypertensinase*, both enzymes, destroy the respective blood pressure elevating substances renin and hypertensin. Unfortunately, considerable difficulty is encountered in the attempted application of this experimental evidence to essential hypertension in man. There are many unexplained features which do not permit its acceptance. This is particularly true of the early phase in the benign stage of essential hypertension.

The neurogenic and vasomotor origin of the essential hypertension finds many advocates. Heredity and environmental factors add support to this concept. There is a wide range of potential stimuli such as cerebral, emotional, peripheral, internal, chemical and environmental. These act as afferent stimuli or direct chemical effects upon the vasomotor center completing the reflex arc or arcs through the sympathetic nerves to the walls of the arterioles. Vasoconstriction results, with the resultant hypertension. Elimination of the stimuli or breaking the arc, if the vasopressor action has not continued to the point where structural changes have been produced in blood vessels or organs, should materially affect the hypertension. Thus, resolution of the emotional and apprehensive problems of the hypertensive individual should benefit the hypertension. Controlling the aggressive and competitive impulses and easing the struggle for existence would contribute materially in removing the cerebral stimuli to the vasomotor center. The surgical approach by the various methods of splanchnic sympathectomy break the arc.

DRUG THERAPY OF HYPERTENSION

The use of the various drugs in the therapeutic armamentarium in the treatment of hypertension can be very well defended if these theories of causation are correct. The sedatives act by decreasing the stimuli produced by emotional problems. They diminish the intensity of the aggressive and competitive impulses. The vasodilating types of drugs are usually of relatively short duration in their activity. However, this is true of almost all drugs used in any treatment. Repetition of dosages is therefore necessary. The drugs can dilate and relax vessels which are relaxable and dilatable. If the purpose is thus to reduce blood pressure they can do so when the conditions are favorable, just as various surgical procedures do with carefully selected patients. The same care in selecting patients for drug therapy as for surgical therapy is necessary if its effectiveness is to be properly evaluated. Drugs should not be condemned as ineffective if pronounced structural changes have already occurred in the blood vessels.

and organs Diminution in heart size, improvement in electrocardiographic evidence and absorption of retinal and intracranial hemorrhages can be obtained from judicious bed rest and drugs. Subjective well-being can be obtained from psychotherapy and a well painted outlook on life despite no change in the blood pressure levels

Those of us, still undecided as to the theories of causation and the uncertainty in treatment to be recommended, may try to combine and harmonize the concepts The philosophy of life expressed by J. L. D may be the best answer to the problem of hypertension for the patient.

J. L. D, a white male bookkeeper, was 43 years of age when he consulted me on January 7, 1943 He gave a history of hypertension of six years' duration, first noticed at the age of 37. The average readings he stated were 220 mm. of mercury systolic and 120 mm diastolic Medicinal treatment and regulation of the way of life produced no improvement.

In March 1940 he underwent a bilateral lumbodorsal sympathectomy and splanchnicectomy performed by one of the leaders in the field of this type of surgery. No change was noted Precordial distress was the major complaint, with severe pain on moderate exertion He had had three severe attacks within the past three months but had continued to work. His eyes were failing There was no nocturia.

The patient was in pain during the office examination The blood pressure reading was 220/130 The eyegrounds revealed tortuosity, silver streaking and periarterial linear exudate No hemorrhages or "cotton-wool" patches were seen. There was slight proptosis The heart rate was rapid, the left heart border was located by percussion at a point 11 cm. to the left of the midsternal line The sounds were distant with a tick-tack type of rhythm The blood count and urinalysis were normal. A slight tremor was present The prostate was small. The deep reflexes were exaggerated The emergency electrocardiogram showed a left axis deviation with left ventricular strain with depression of S-T junction in IV F and T inversion in the same lead Hospitalization was advised on the basis of an actual or an impending acute myocardial infarction The patient decided to wait two days before entering the hospital in order to complete some necessary business, so the following prescription was given

R	Phenobarbital		500
	Papaverine Hydrochloride	3	200
	Erythryl Tetranitrate	8	
	Phenacetin	8	
	Aminophylline	4	
	Mix and divide into 30 capsules		

Sig Take one every four hours

When the patient appeared at the hospital he was much better in so far as his pains were concerned The blood pressure was 140 mm of mercury systolic and 100 mm diastolic The same evidence was found in the electrocardiogram taken in the hospital In fact, several tracings taken since remain the same except that the cardiac rate was reduced to 80 per minute He remained in the hospital for two weeks No further evidence could be adduced The blood pressure under the rest regimen was between 140/100 and 160/110

Office visits were resumed one month after the initial visit. The patient did not have a recurrence of his precordial pain nor has he had since, but his physical activities have been considerably curtailed. He has nevertheless continued to work His pressure rose to 180/110 Then the erythryl tetranitrate in the prescrip-

tion was raised first to 400 mg. and then to 500 mg. for the thirty capsules. The pressure was maintained about 158 to 160 mm. of mercury systolic and 100 to 106 mm. diastolic. In January 1944, while he was still on the medication, his pressure reading was 200/120.

Sodium nitrite, 2 gm. was substituted in the prescription for the 500 mg. of erythrityl tetranitrate in the thirty capsules. The therapy showed no effect on the hypertension. An increase in the phenobarbital to 1 gm., the other constituents remaining the same, produced no effect. Mannitol hexanitrate was the next substitution for the vasodilating drug. One gram was used in place of sodium nitrite. A trial of two months revealed no objective improvement in the blood pressure reading. The patient was thoroughly and actively interested in the therapeutic experiment throughout the trials of the various drugs. His insistence on therapy was the major motivating factor in the various decisions.

An extensive experience with the thiocyanates has produced sufficient conviction that, in addition to the central nervous system sedation, histotoxic effect is a major pharmacologic action. The improvement in the blood pressure reading is thus the result of a poisonous activity which can be stimulated by many drugs if toxic doses are employed. If this method of approach is followed, reasoning then indicates that minimum rather than maximum intake should be advised to effect diminution in the blood pressure. There is thus little justification for the attempts to raise the blood thiocyanate levels to 10 to 15 mg. per 100 cc. Too frequently under high dosage and high blood levels toxic psychoses, acute cerebral accidents and fatal cardiac episodes ensue. Patients must be carefully selected. Those with evident renal, cardiac or cerebral complications are poor candidates for this mode of drug therapy. The individual in the older age group does not bear this type of treatment well, although individualization is permitted. Patients with excessively high diastolic readings probably should not be subjects of sulfocyanate therapy. Personal experience suggests that small doses long continued, with blood levels of 3 to 5 mg., will accomplish more and be less dangerous. *Primum non nocere* (first do no harm) is a therapeutic maxim which can still bear repeating.

J. L. D. was given his trial of thiocyanate in the following prescription:

- R Sodium Phenobarbital
Potassium Sulfocyanate
Potassium Bromide
Lixa Beta
Mix and shake.

1941
1942

Sig. One teaspoonful in water after meals and at bed.

He was instructed to telephone if any unusual effects were felt. After six months treatment the pressure readings were 158 mm. systolic and 106 mm. diastolic. The blood level of sulfocyanate was 3.5 mg. per 100 cc. The therapy has been continued for a little over a year. The last blood pressure reading in June 1944 was 158 mm. systolic and 110 mm. diastolic. A definite fall in blood pressure was noted.

of May 14, 1946 continued the evidence revealed on the first examination. Adequate sleep was obtained by added sedation (chloral hydrate) when indicated. The patient's life runs smooth and even. He is satisfied in that he can support his family of three children on his salary as a bookkeeper. He insists on monthly visits to the office. He assumes the attitude "I have done all I could do. I am satisfied. I have tried everything. You must keep me going as long as you can so that I can raise my family. If something new comes along, try it on my blood pressure. If there are any other drugs you think have value let's use them all." The "spes hypertensica" in this patient is certainly characterized by a scientific attitude, in that he will willingly submit his hypertension for experimental purposes. The case also illustrates the hopeful prospects which severe hypertension so frequently offers the hypertensive patient.

We recall Osler's admonition to the physician on prognosticating the outlook to the patient with angina pectoris. "Rather quote him the case of John Hunter who died twenty years after his first attack than that of Thomas Arnold who dropped dead in his first episode."

CORONARY DISEASE

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CORONARY disease and arteriosclerosis of the coronary arteries are terms commonly used to designate what is properly called atherosclerosis of the coronary arteries. In the early stages of this progressive disease, foam cells containing cholesterol accumulate in the sub-endothelial layers of the intima. This type of lesion may develop in infancy, has even been reported in the newborn. The lesions are not often found in those 20 to 30 years of age but become more numerous with advancing years. In childhood and puberty they may be reversible. As the cholesterol deposits increase in size, nutrition is impaired, the deep layers undergo necrosis, and scar tissue develops. Still later, calcium salts may be deposited in the atherosclerotic lesions. Another change which may develop in connection with these aged-scarred subintimal cholesterol deposits is necrosis of the intima covering them as a result of subintimal hemorrhages or pressure obliteration of the vasa vasorum. Intimal necrosis is followed by thrombus formation and occlusion of the artery.

Coronary atherosclerosis causes narrowing of the arterial lumen and therefore more or less ischemia of the myocardium long before occlusive thrombi develop. Myocardial ischemia causes necrosis of muscle fibers which are replaced by strands of scar tissue. An occlusive coronary thrombus usually causes myocardial infarction, but when the collateral circulation is adequate, it may cause only an increase of the fibrotic changes that ordinarily follow narrowing of the lumen.

Surveys of necropsy records show that some 70 per cent of men over 50 and women over 60 have more rather than less coronary atherosclerosis, that almost 100 per cent of men and women over 70 years of age suffer from this disease. Some 45 per cent of the deaths of all over 50 years of age are due to coronary atherosclerosis.

Coronary disease can and should be suspected as a direct or contributory cause of disability in all men past 50 and women past 60 years of age. It must also be considered in those in younger age groups who have long had persistently elevated blood pressure or diabetes mellitus.

SYMPTOMS

The earliest symptoms of this progressive and almost universal arterial disease of advancing years are those of the heart failure it causes. One such symptom is gaseous distention of the abdomen due

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to portal congestion which is too often ascribed by physician and patient to indigestion, constipation or gallbladder disease. Precordial pressure or a feeling of fullness after moderate exertion following a meal, especially a heavy one, are also often ascribed to disorders of the digestive system. But even when there are no significant electrocardiographic changes, when the heart is normal in size on physical and x-ray examination and when gallbladder or other digestive tract disease is found, myocardial fibrosis as a result of coronary atherosclerosis may contribute to the genesis of symptoms.

Sometimes the first evidence of the coronary disease is a cough which does not amount to much during the day but is quite aggravating at night. Sleeplessness, even in the absence of a cough or of any difficulty in breathing of which the patient is aware, may be due to beginning pulmonary congestion and orthopnea. Too often in such cases a diagnosis of chronic bronchitis is made. Paroxysmal nocturnal dyspnea is too often confused with bronchial asthma.

Symptoms such as these are frequently present only during the winter months or after rapid sudden changes in temperature or barometric pressure, when contraction of the peripheral arteries makes greater demands upon the heart. Breathlessness on exertion and dependent edema are also more pronounced under such conditions, even though the patient remains at rest and indoors all of the time. Many believe, however, that angina pectoris, the angina of effort due to spasmodic narrowing of the coronary lumina and myocardial ischemia, is the only symptom of coronary artery disease aggravated by cold or by sudden changes in the weather. Anemia, high altitudes and oxygen want may also cause these symptoms. During the summer months when patients can and do become more active physically, their symptoms are often relieved only to recur when the weather gets cold in the fall.

The angina of effort often appears first after a large meal or on a bitterly cold day when one hurries to keep some appointment or to keep warm, more rarely after some unusually severe and prolonged exertion. It clears up promptly with rest. Standing still for a minute or so usually suffices and the pain does not recur if the individual proceeds more slowly. Unusually severe and prolonged exertion in the bitter cold, not stopped when the precordial pain begins, may cause such severe and long lasting spasm of the coronary artery that an ischemic infarct of the myocardium develops without the formation of a thrombus.

Though physical or mental exertion is almost invariably a cause of angina pectoris, such effort, in the opinion of most writers on the subject, has nothing to do with the formation of a thrombus on an atherosclerotic plaque in a coronary artery. Yet angina of effort developing after relatively slight exertion—no more than has been

regularly performed day in and day out by the particular individual—may be the first symptom of coronary thrombosis. The clot forms slowly while blood flows rapidly over the necrotic intima covering the atherosclerotic lesion, but, because the clot narrows the lumen and causes myocardial ischemia, slight exertion may indicate the angina of effort. Sometime later, a few minutes to three or four hours, the classical symptoms caused by complete occlusion of a coronary artery, with or without pain, develop because the clot has completely blocked the vessel. The thrombus started to form before the exertion supposed to have caused it was performed. The subsequent angina of effort was due to myocardial ischemia from a partially occluding thrombus, not to arterial spasm. The effort did not affect the rate of clot development.

The symptoms, when the thrombus completely occludes the coronary artery, are not influenced by what the patient happens to be doing at that moment. The patient sitting quietly at home may have just as much agonizing and persistent precordial pain radiating to the left arm, to the abdomen or to the neck, just as severe breathlessness, just as much "shock" and fear of impending death as does the man whose thrombus becomes occlusive while he is performing either his usual or some unusual task. Both get increases in the blood count, sedimentation rate and temperature, but neither is more apt to develop hypotension, a pericardial friction rub, mural thrombi, or any particular type of arrhythmia. Nor does what they were doing at the time the occlusion became complete, determine whether or not the heart will rupture, will develop an aneurysmal dilatation, anginal or congestive heart failure or a small scar and little impairment of function. However, what the patient does after the occlusion is complete and the infarct has developed, may influence the subsequent healing and the size of the scar.

Before discussing the treatment of coronary thrombosis and the damage it causes to the myocardium, mention must be made of the fact that coronary atherosclerosis, with or without the formation of occlusive thrombi, may so limit the myocardial blood supply as to initiate paroxysms of any type of arrhythmia and may cause them to become permanently established.

DIAGNOSIS

Coronary disease by causing myocardial fibrosis induces changes in the electrocardiogram some of which are pathognomonic but most merely suggestive. Progressive changes in graphs made at intervals of months or years are more significant than the changes from "normal" in a single graph, just as the changes that develop from day to day following an acute coronary occlusion are more significant than those found in one graph. No attempt will be made at this time to describe the electrocardiographic changes which may be due to coronary

disease. The value of periodic graphs of patients old enough to have much coronary disease cannot be overstressed. More information can be obtained if, in addition to the standard limb leads, leads CF_2 , CF_4 and CF_5 are regularly taken and still more if all unipolar chest leads are used.

Though coronary disease may of itself cause hypertrophy and dilatation of the heart, there may be no demonstrable changes in the size and shape of the heart and no significant alterations in the electrocardiogram the day before an occluding thrombus develops. Later in the course of the disease emphysema, whether due to, or the cause of myocardial failure, makes it difficult to determine the size of the heart with any degree of accuracy by physical examination. Murmurs may or may not be heard and are not necessary for diagnosing coronary disease. The pulse rate is usually within normal limits though it speeds up unduly on exertion and takes longer than it should to return to normal. Coronary disease may cause any of the arrhythmias.

While those with hypertensive cardiovascular-renal disease have more coronary atherosclerosis than do others in the same age group, an elevated blood pressure is not characteristic of coronary disease. The blood pressure may be low or normal. In older people whose arteries and aorta have lost their elasticity and become tortuous and elongated, the systolic pressure may be quite high but the diastolic within normal limits, regardless of the amount of atherosclerosis present.

In making an early diagnosis of coronary disease the history is of utmost importance, for physical signs are apt to be conspicuous by their absence. Changes in the electrocardiogram may be significant but should not be the sole basis for making this diagnosis. In the more advanced cases with pulmonary congestion or other symptoms of heart failure, but no coronary thrombosis, the absence of evidence of rheumatic, syphilitic or other type of heart disease helps establish a definite diagnosis. It is difficult to make a diagnosis in those under fifty years of age unless they have typical coronary occlusion, long-standing hypertension or diabetes mellitus.

Since coronary disease is quite common in the fifth and sixth decades and since many elderly patients with rheumatic and syphilitic hearts develop heart failure and die without activation of the underlying disease or infection, may such failure not be due to the imposition on a long-diseased myocardium of a little fibrosis due to the ischemia of coronary disease? In such hearts the factor of safety is so slight that a minimal destruction of muscle cells due to ischemia would cause heart failure.

TREATMENT

Coronary Atherosclerosis and Myocardial Fibrosis; Healed Myocardial Infarction.—Until more is known of the etiology of atherosclerosis little can be done to prevent it or alter its course. It

has probably been present for many years before it begins to cause symptoms, the first of which may be a dramatic fatal coronary occlusion. Yet much can be done to enable a patient to live actively, comfortably and happily for many years with this disease. Such management can be most effectively given by a physician who individualizes treatment as did the immortal "family doctor" who knew so much less about disease.

The patient with minimal symptoms or who, chiefly because of age and family history, may be regarded as having potential coronary disease, is advised to slow down a bit, to abstain from the more violent forms of sport unless he is able to engage in them regularly all the year round, to take more vacations and keep more regular hours, to avoid activities that cause him to be overtired, short of breath or to have discomfort in his chest. He should, however, take walks or engage in sports requiring little exertion.

The diet should contain all essential nutrients and enough protein, carbohydrate and fat to maintain him in nitrogenous equilibrium at a weight normal for one of his height and build. If overweight, he should reduce slowly by limiting intake of fats and carbohydrates and partake of a "snack" in the latter part of the afternoon to prevent hypoglycemia. Patients are advised not to add salt to their food at the table. Fresh meats, fish and fowl are not restricted.

Patients often fear that smoking will be arbitrarily forbidden. This may not be necessary as nicotine seems to cause symptoms only in people who are sensitized. It does not cause coronary disease. If smoking may aggravate the symptoms in a patient, ask him to forswear the pleasure for a couple of weeks in order that the effects of its withdrawal may be determined. He is told that if he does not feel much better he will be permitted to smoke, though fewer cigarettes may be advised. If he feels better as a result of the two weeks abstinence, he will be convinced that he should swear off permanently.

Patients also ask about coffee. I tell them that the xanthines extensively used in the treatment of coronary disease are very similar to caffeine and more potent as far as effects on blood vessels are concerned but less stimulating to the nervous system. Coffee with cream may upset digestion and cause distress. If it agrees it may be permitted at breakfast, possibly at lunch, but both coffee and tea should be avoided during the afternoon and evening as they may prevent restful sleep.

Another stock question has to do with the use of alcoholic beverages. Alcohol is a vasodilator and so should be of value in the treatment of coronary disease. It is more valuable as a sedative and is less injurious than many of the drugs used for that purpose. A hot toddy before going to bed is one of the most effective sleep producers we have. If you are sure that the patient will not take more than you prescribe,

a cocktail or highball before dinner is of great help in getting him to relax so that he may enjoy his dinner and be ready to go to sleep when the time comes. Some patients feel that a good drink of whiskey is the most effective remedy for angina of effort and use it in preference to nitroglycerin. In spite of its beneficial effects when used judiciously, it must be forbidden to those who cannot drink with moderation and to those hypertensive patients whose blood pressures go up when they are consuming alcoholic beverages regularly.

The preparations of *theophylline* and *theobromine* are of value because they increase coronary blood flow. Their regular use during the winter months prevents many symptoms that otherwise will develop. They are of especial value in relieving and preventing angina and nocturnal paroxysmal dyspnea. In larger doses they are effective diuretics. *Aminophylline* and *theocalcin* cause less gastric distress than do other xanthines.

When heart failure with systemic or pulmonary congestion develops, *digitalis* is a valuable remedy even though it does reduce coronary flow as it improves myocardial tone and increases cardiac output. If a xanthine is given at the same time, the effect on coronary flow is neutralized. If auricular fibrillation has developed, *digitalis* should be administered in full doses to slow the ventricular rate provided quinidine will not cause restitution of normal rhythm. When the xanthines plus bed rest and *digitalis* do not overcome the congestive heart failure the mercurial diuretics, especially when combined with xanthines, may be administered preferably by intramuscular injection. *Digitalis* should be discontinued two or three days before these diuretics are administered, as its concentration following diuresis may be sufficient to make it toxic.

Nitroglycerin is the remedy par excellence for the treatment of angina of effort. It is inexpensive, effective and not toxic or habit forming. Its effects last only a few minutes. It is of value not only for the prompt relief of pain but also for the prevention of anginal attacks. Patients not infrequently complain of a feeling of fullness in the head after taking 0.65 mg (gr. 1/100) of this rapidly acting drug. It is therefore advisable to start with doses of 0.32 mg (gr. 1/200) to 0.47 mg (gr. 1/150) which will usually prevent or relieve anginal pain and not cause the distressing after-effects. Patients who have the anginal syndrome, before or after coronary occlusion, learn what activities will precipitate the precordial pain. If *nitroglycerin* is taken just before it is necessary to perform these activities there will be no pain. *Nitroglycerin* is also of value for the relief of paroxysmal nocturnal dyspnea.

Rest is popularly believed to be essential for the proper treatment of heart disease of any sort. Rest is important, but except for six weeks following an acute coronary occlusion with cardiac infarction

or a complicating infection, complete bed rest for long periods is rarely indicated. After a coronary occlusion it is advisable to permit the patient to use a commode as it requires less effort than does the use of a bed pan. When bed rest is indicated, it is advisable to raise the patient to a near-sitting position (with pillows or a bed rest under the mattress) as breathing is much less difficult in that position. Some patients with severe congestive heart failure can sleep only while sitting in a chair and leaning forward to rest the head on a hospital bed, the back of a low armchair or a table.

Older people with coronary disease should be kept in bed for as short a time as possible, since complete rest may cause the circulation to become so sluggish that thromboses are apt to develop. One must be on the lookout for thrombophlebitis or phlebothrombosis as well as for arterial and mural thrombi. Active or passive motion of the extremities, light massage and frequent turning of the patient will help prevent venous thrombosis.

The amount of rest required must be determined by the condition of the patient. Alternating periods of rest and exertion are often more effective than complete rest. With ambulatory patients, midmorning, midafternoon and postprandial rest periods are especially valuable. Lying down for from fifteen to thirty minutes to get complete relaxation is valuable at such times. But the patient need not sleep during the rest periods. In fact it is often better that he does not, as too much sleep during the day makes it difficult to sleep at night.

Acute Infarction—Following an acute infarction, *complete bed rest* (the use of a commode may be permitted after the third day) is indicated for a period of six weeks that the size of the scar may be as small as possible and to give time for the formation of a firm scar in all parts of the infarct. Shorter periods of rest are apt to result in more extensive scarring and in aneurysmal dilatations of the ventricle. After the six weeks of complete rest, the patient is permitted to sit up for a few minutes at first once, then twice to four times a day. This method is much better than permitting the patient to be up only once and gradually lengthening that period. After he is able to sit up for twenty minutes or so, three or four times a day, each period is prolonged but not by enough to cause fatigue or other symptoms of heart failure. Then comes gradually increasing physical exertion followed by shorter and shorter and then less frequent rest periods but always avoiding anything that causes discomfort.

Characteristically the pain of cardiac infarction is not relieved by nitroglycerin or other vasodilator drugs. *Opiates* and *oxygen* are indicated and should be administered as needed to keep patient comfortable. Papaverine is sometimes very effective, but morphine with atropine is most effective. Aminophylline, 100 mg by mouth, should be started at once and administered every four hours.

Recently there have been several papers on the use of *heparin* and *dicumarol* for the prevention of further coronary and of mural or venous thrombosis. This therapy is still on an experimental basis and not ready for general use.

In some clinics, *quinidine* is used routinely to prevent ventricular tachycardia and fibrillation but its effectiveness has not been definitely established. Because of its vasoconstrictor effect digitalis should not be used unless congestive heart failure or auricular fibrillation develop. Even then it should not be administered in large doses such as are used to get rapid maximum effects but in doses of one cat unit daily.

When the use of opiates is no longer required for the relief of pain, it is usually necessary to give sedatives if enough rest is to be obtained during the first two to three weeks after the occlusion. Which sedative or hypnotic is to be used will depend on how the particular patient reacts, on whether the particular sedative causes restful sleep or sleep disturbed by dreams. Their use to obtain complete rest is indicated until there has been time for scar tissue to grow in from the periphery of the infarct and form a firm scar at its center. This takes from fifteen to eighteen days.

Though the etiology of coronary disease is unknown and its treatment, through the use of vasodilators and drugs increasing coronary blood flow and teaching the patient how to live with the disease, is palliative, there is evidence that people with it are living longer (1). In spite of the increase in the number of deaths it causes, corrected rates indicate that the death rate for the principal cardiovascular diseases is falling in all except the 35 to 54 age groups (2). Most cardiovascular disease deaths in people over 54 years of age are due to the effects of atherosclerosis, so the decline in the death rate from these diseases in those age groups, small as it is, indicates that the non-specific therapy now being used, is reasonably effective.

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THE ASSOCIATION OF GALLBLADDER DISEASE WITH HEART DISEASE: CLINICAL AND EXPERIMENTAL OBSERVATIONS

HOWARD WAKEFIELD, M D *

THE association of organic heart disease and disease of the biliary tract, especially cholecystitis with stone, has been observed and emphasized many times by clinicians since the middle of the nineteenth century. It is common clinical experience to see gastrointestinal disturbances mimic cardiac ailments perfectly, and conversely to see cardiac disease reflect itself in disturbances of the gastrointestinal tract and the biliary system. For example, recently I saw a 60-year-old white woman who gave a perfect history of acute coronary thrombosis. Further study and clinical observations together with gallbladder and gastrointestinal x-ray studies indicated, however, that she had an esophageal hiatus hernia. If I had had to depend on this patient's history and physical examination alone, I would have been warranted in treating her for acute coronary thrombosis. Parenthetically, esophageal hiatus hernia and acute coronary thrombosis may coexist, as in one of my patients in whom the coronary occlusion was fatal.

The cardiovascular and gastrointestinal systems are closely related anatomically and physiologically. Both systems are innervated by the sympathetic and parasympathetic nervous systems and both are subject to reflexes in either of these systems. The gallbladder is supplied by the left vagus nerve and also by sympathetic fibers from the celiac plexus.

In 1907 David Riesman reported two patients in whom apical systolic murmurs occurred during attacks of gallstone colic. He also found that the heart was dilated during the attacks. After an attack the murmurs would disappear and the heart would return to its original size. Very few observations have been reported, as far as I know, confirming these findings.

What is the mechanism for the production of the systolic murmur at the cardiac apex during gallstone colic as reported by Riesman? May it not be due to the dilatation of the heart during the acute episode? Certainly systolic murmurs are heard at the cardiac apex in congestive heart failure associated with dilatation.

In 1909, Robert Babcock, a blind physician of Chicago, published his classic paper in which he cited many cases of organic heart disease, especially angina pectoris, which were benefited by the removal of

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the diseased gallbladder In 1924, Hamburger and Straus reported patients in whom disturbances of cardiac rhythm of long standing were cleared up by removal of the stone-bearing gallbladders

In 1935, Wolterth and Fitz-Hugh reported six patients with coronary patterns in their electrocardiograms, all of which returned to normal after removal of the stone-bearing gallbladders These are important observations and are apparently the first to be recorded in the literature.

The physiological approach to the gallbladder-heart relationship was made in the 1920's by Carlson, Luckhardt, Ivy and others, who demonstrated the presence of viscerocardiac reflexes in frogs, turtles and dogs Gilbert, Fenn and their associates have demonstrated in the dog a decrease in the coronary blood flow upon distention of the gallbladder

ILLUSTRATIVE CASES

CASE I—The first patient is an 86 year old white man who had typhoid fever while serving as an officer in the Spanish-American War Because of acute gallbladder colic, in 1912, his gallbladder was drained—the operation of choice at that time For the past thirty years he has had subacute attacks of gallbladder colic upon eating too much, especially of fatty foods These attacks have usually been less severe than his original attacks, manifesting themselves as a rather constant dull pain confined to the right upper abdominal quadrant At times the attacks have been accompanied by one or two degrees of fever, but no chills, jaundice or clay-colored stools

During the past twenty years I have observed this man with three to four such attacks each year As he is thin, it is usually easy to feel his distended gallbladder during the attacks Whenever his gallbladder has been distended I have heard frequent extrasystoles in his heart—usually a ventricular premature contraction every third or fourth beat. These extrasystoles usually persist as long as the gallbladder remains distended—anywhere from twenty-four to forty-eight hours As the distention subsides, the extrasystoles disappear and the patient begins to feel more comfortable When he has been well, I have always found a regular rhythm in his heart, with no extrasystoles

In the last two years this patient has very gradually developed angina pectoris If he walks too fast, or immediately after a meal or against a cold wind, a dull sub-sternal pain occurs It is so severe as to force him to stop walking

This patient's electrocardiogram has been normal for a man of his years, and the tracing has been consistently the same for the last fifteen years There is no history that suggests a possible myocardial infarct. There are many clinical and experimental observations which indicate that the extrasystoles in such a patient are produced by the stimuli arising in the distended gallbladder The premature contractions are a good example of viscerocardiac reflexes, in this case, mediated through the vagus nerve

What part has the diseased gallbladder, which the patient has carried for thirty-five years, played in bringing on the angina pectoris in these last two years? In the light of more recent experience (Case II) it is probable that if a cholecystectomy had been performed in

1912 it would have prevented the development of an angina of effort. On theoretical grounds at least one of the extrinsic cardiac factors in the production of angina would have been removed, i.e., the diseased gallbladder.

CASE II.—The second patient is a thin (118 pounds) 22 year old white woman, the mother of a 2 year old baby. For the past two years she has complained of a dull aching pain in the upper right abdominal quadrant. The pain has never been acute and has never required medication. There is no history suggesting acute gallbladder colic. Only a large meal seems to aggravate the pain. During these past two years she has also complained of her heart jumping and pounding in her chest. She was examined by several physicians who told her that her heart beat was irregular. The irregular heart action has bothered her more than the abdominal pain.

On physical examination the gallbladder region was found to be slightly tender and the heart had frequent extrasystoles. The heart was not enlarged and there was no evidence of organic heart disease. Blood pressure was 118/80. Gallbladder visualization showed many stones. Upon cholecystectomy the gallbladder was found to be completely buried in adhesions between the transverse colon and the liver margin. It was large and filled with stones of assorted sizes. During the first postoperative day her cardiac rhythm was perfectly regular and not once during the entire postoperative period did I hear any premature contractions, nor were any detected during subsequent observations by the house officers. The cholecystectomy was performed on February 29, 1944, and for two years she has been free from any irregular heart action.

It is evident in this case that the cholecystectomy stopped the extrasystoles almost immediately. Whether it will prevent the later development of angina is of course conjectural. From a physiologic viewpoint it appears that the cholecystectomy removed the source of the stimuli for the production of the extrasystoles. In the gallbladder-heart reflex, with the vagus nerve acting as the mediator, the removal of the gallbladder destroys one source of extracardiac influences which may disturb cardiac rhythm.

Just recently White and his associates in an extensive necropsy survey showed that gallbladder disease occurred almost twice as often in patients with coronary artery disease as in those with normal coronary arteries.

CASE III.—This patient, a white woman of 67 years has a history of angina pectoris of twenty years standing, with frequent recourse to nitroglycerin. The presence of gallstones was considered a possibility fifteen years ago. She also has had two recognized coronary occlusion one attack seven years ago and the other attack four years ago. Serial electrocardiograms during these two acute episodes indicated that myocardial infarction had occurred. She also has a history of high blood pressure of at least twenty years duration. Recent observations indicate that her blood pressure varies between 170/90 and 220/104. A younger sister died of acute coronary thrombosis.

During the past twenty years there have been only two episodes which might be interpreted as attacks of acute gallbladder colic. However the patient has had a great deal of dull aching pain in the upper right abdominal quadrant and she cannot properly digest fatty foods of any kind. During the past year the substernal pain on walking has been so severe that frequently she has used five to six $\frac{1}{400}$ grain tablets of nitroglycerin under her tongue to relieve the chest pain.

This patient is thoroughly posted about the nature of all her ailment and is willing to do anything the doctors recommend in order to avoid her sister's fate. A thorough preoperative study of her physical condition was made and no evidence of congestive heart failure was found. The heart beat was irregular, with premature ventricular contractions every eight to ten beats. Cholecystectomy was performed and she had a very smooth, uneventful postoperative recovery. On her third postoperative day she stated that she had a "lightness" in her chest which had not been present for twenty years. She can now walk a block with little or no substernal pain and nitroglycerin is seldom used.

Cholecystectomy in this patient has produced the most dramatic amelioration of anginal pain I have ever seen. I do not think for one moment that we have cured her angina pectoris, for I am quite sure that if she walks too fast, or immediately after a full meal or against a cold wind, her anginal pain will return, probably in a severe form. Certainly, however, the cholecystectomy has subdued her effort pain on walking at an ordinary pace which she could not do in comfort before her gallbladder was removed. Naturally the patient is gratified (almost beyond her expectations—and our own, too!) at the unusual degree of relief she has received from the gallbladder operation. Although the surgical risk in a patient with such a cardiac background is grave, yet with good teamwork on the part of the internist, the surgeon and the anesthetist, many patients with serious cardiac conditions can be carried through cholecystectomy successfully.

It is obvious that before operation, the internist must make a thorough appraisal of the whole body, with special emphasis on the current status of the cardiovascular system. If there is any physical evidence of congestive heart failure, even of the slightest degree, elective surgery should be postponed. Internists and surgeons who take such great risks will certainly have a high surgical mortality. Recently I have heard of two patients who had a slight degree of congestive heart failure about two months after coronary thrombosis. Both patients were operated on for gallstones during the heart failure and both died early in the postoperative period.

Occasionally, of course, the surgeon is justified in risking operation in emergency cases even when serious cardiac states exist. I know of two instances in which acute appendicitis occurred during the third week of myocardial infarction following acute coronary thrombosis. The surgical risk was great, yet both patients survived the appendectomy and went on to recovery from the myocardial infarction. They were fortunate, indeed, for the outcome might very well have been death. In elective cases the surgeon cannot afford to take the risk.

It is my conviction that in coronary artery disease and its most common clinical manifestations, either angina pectoris or healed myocardial infarcts, associated with chronic gallbladder disease, with or without stones, cholecystectomy should seriously be considered, provided the patient's cardiac status warrants the surgical procedure.

The physician should explain frankly to the patient the true situation, pointing out that removal of the gallbladder will not cure his angina, but that the anginal pain may be alleviated. It should be emphasized that we have no accurate means of determining how much of the anginal pain is due to the heart and how much is due to overlapping gallbladder disease. We remove the gallbladder and see how much residual anginal pain remains. After cholecystectomy one must not be too hasty in drawing conclusions as to how much relief the patient has obtained from his angina pectoris. Often many months must go by before the physician can properly evaluate the result.

CASE IV—This patient is an obese 215 pound white man of 46 years. His blood pressure has varied between 158/100 and 220/130 since 1944. In March 1944 he had a definite anterior myocardial infarction. During the following year a degree of congestive heart failure was evidenced by basal râles in both lungs and a moderate amount of edema of both legs together with shortness of breath on walking but no chest pain. Gastrointestinal x ray studies show the scar of an old healed duodenal ulcer and a large solitary stone in the gallbladder.

Since the episode of coronary thrombosis in 1944 the patient has had three attacks of acute epigastric pain which required morphine for relief. During these attacks the gallbladder region was definitely tender and there was residual tenderness in the gallbladder for twenty four to thirty six hours after the epigastric pain had subsided. Both the clinical and laboratory evidence in this case confirm the coexistence of gallstone disease and coronary thrombosis. Hypertension and obesity are in the clinical picture also.

In this case we have so far avoided gallbladder surgery, because of the clearcut evidence of congestive heart failure following coronary thrombosis. The presence of congestive heart failure, as I have mentioned, definitely contradicates a surgical approach at this time. An attempt is being made to build up the cardiac reserve by adequate rest, digitalis and coronary vasodilators and the great importance of a weight-reduction program is emphasized to the patient. If his cardiac status definitely improves later and the gallbladder is still causing trouble, cholecystectomy may be seriously considered.

I am impressed with the number of patients I see with acute coronary thrombosis, in whom, at a later date, gallstones are found. These persons suffer an acute coronary thrombosis with all the usual clinical and laboratory evidence of acute myocardial infarction and then, one, two or three years later, experience another acute episode of severe epigastric pain. In such instances, my first impression is always that we are dealing with another episode of acute coronary occlusion, but further study often identifies the subsequent attack as one of gallstone colic. Occasionally I have seen such conditions progress to acute empyema of the gallbladder. After the gallbladder has been permitted to "cool off," cholecystectomy has been performed with good results in the majority of cases.

In many patients with associated gallbladder and coronary artery

disease, the disease of the gallbladder with its stones is a much older pathologic process than the coronary thrombosis with its resultant myocardial infarction. It is curious in many of these cases, too, how long the diseased gallbladder is "silent." Although the stone-bearing gallbladder may not be producing acute colic, the stimuli arising from it may be supposed to have some effect on the coronary blood flow and the coronary circulation. Just how much the diseased gallbladder and its stones play in the immediate precipitation of acute coronary thrombosis remains a question.

From the foregoing it is evident that all patients with coronary artery disease—i.e., angina pectoris or coronary thrombosis with myocardial infarction—should be thoroughly studied, especially by x-rays of the gastrointestinal tract and gallbladder, to rule out the possibility of esophageal hiatus hernia, duodenal ulcer and gallstones or non-functioning gallbladder. As Gilbert emphasizes, esophageal hiatus hernia is still underdiagnosed. It is still true in medicine that we find what we look for, and the more one sees of such cases, the more strongly he comes to feel that the heart, gallbladder and stomach form an intimate triad.

EXPERIMENTAL FINDINGS

During the past three years Dr. S. W. McArthur and I have been studying electrocardiographically the effect on the heart of the distended gallbladder in human beings. Throughout the operation of cholecystectomy the patient is connected with the portable electrocardiograph. After the gallbladder is isolated, especially in those cases in which a stone is jammed into the cystic end of the gallbladder, 30 to 50 cc. of normal salt solution is injected rapidly with a needle and syringe through the fundus of the gallbladder and the effect of the distention is recorded on Lead II of the electrocardiogram.

In cases in which the stone is tightly wedged in the cystic end of the gallbladder, a high degree of distention is produced. In studying twenty-five patients so far, we have observed disturbances of rate, rhythm and conduction, as recorded in the electrocardiogram. Briefly stated, the following changes have been noted: (1) *Prompt increase in heart rate*. In the great majority of our patients the distention of the gallbladder speeds up the heart rate. Slowing of the heart rate, or bradycardia, has not been observed in our series. (2) *Extrasystoles*. The most common disturbance of rhythm recorded is extrasystoles—premature ventricular contractions. The extrasystoles occur in the majority of cases and in some patients the premature ventricular contractions are frequent. When the distended gallbladder is relieved by suction with a syringe the extrasystoles disappear immediately. (3)

Prolonged auriculoventricular conduction time (increased P-R interval) occurs fairly frequently. A shortened P-R interval has been seen in some patients and occasionally the P wave may disappear entirely. Complete heart block was produced in one case and ventricular tachycardia of short duration was observed in one patient. T_2 has been depressed to the isoelectric level in many instances, but complete inversion of T_2 has not been seen. In our control tracings taken during

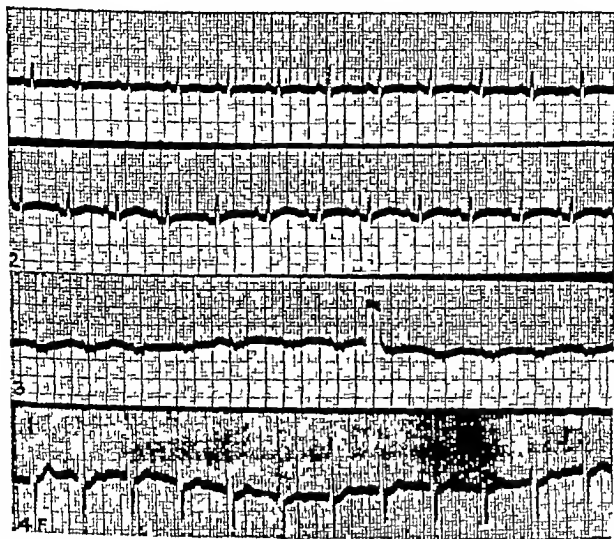


Fig 15—White man, aged 73. History of gallbladder colic for ten years. Electrocardiogram taken just before gallbladder was completely distended during gall bladder colic.

the third plane of anesthesia before any surgery was done, we have seen very little disturbance of heart rhythm.

Our observations so far indicate that it is impossible to predict what will happen in the electrocardiogram after distention of the human gallbladder. There is no specific reaction or pattern that is characteristic of gallbladder distention. In some instances distinct and rapid changes occur immediately after distention of the gallbladder with normal salt solution, in others, little or none.

In all experimentation, and certainly in biologic experimentation, we should attempt to set up our experimental conditions to mimic nature as closely as possible. For example, distention of the human gallbladder occurs in both physiologic and pathologic states and distention of a hollow viscus like the gallbladder is usually an adequate test stimulus. Certainly traction, cutting, pinching, thermal and electrical stimulation do not occur in the human being in the natural course of events.

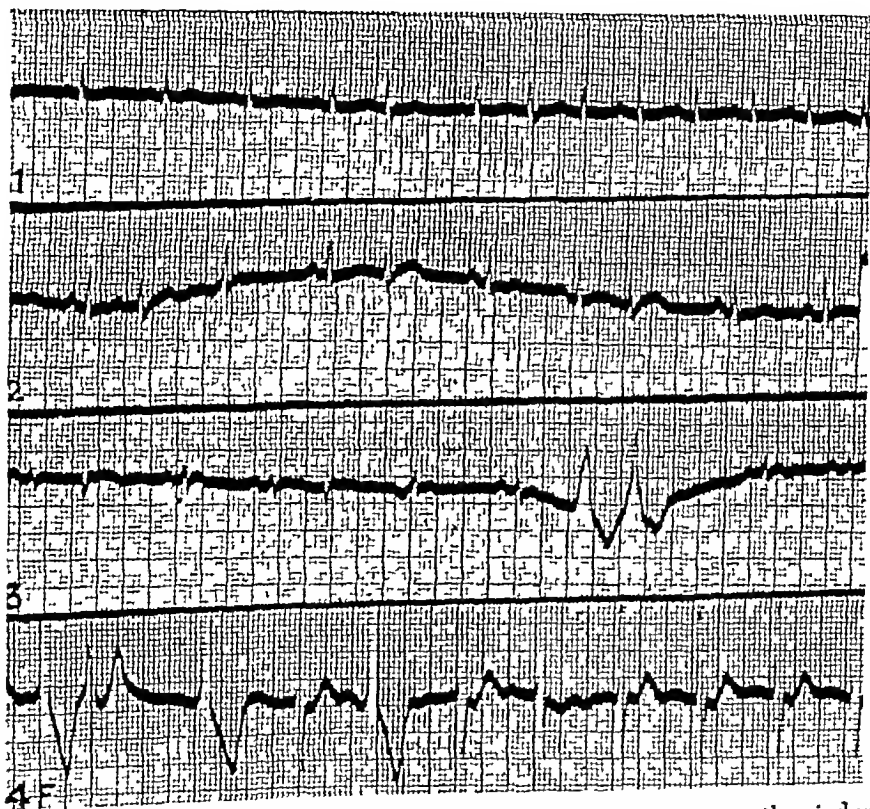


Fig 16—Electrocardiogram at height of distention. Patient was a thin individual and the gallbladder could easily be palpated. Tracing shows increased heart rate, extrasystoles, short runs of paroxysmal auricular tachycardia and some depression of amplitude of the T waves.

The reaction in the human heart as recorded by the electrocardiograph after distention of the gallbladder may be a vagus effect. In the experimental animal such as the dog, frog and turtle, the vagus connection between the heart and gallbladder has been well established by the work of Carlson, Luckhardt and Ivy. When both vagi are sectioned or paralyzing doses of atropine are used in the experimental animal, nothing happens in the heart when the gallbladder is suddenly distended.

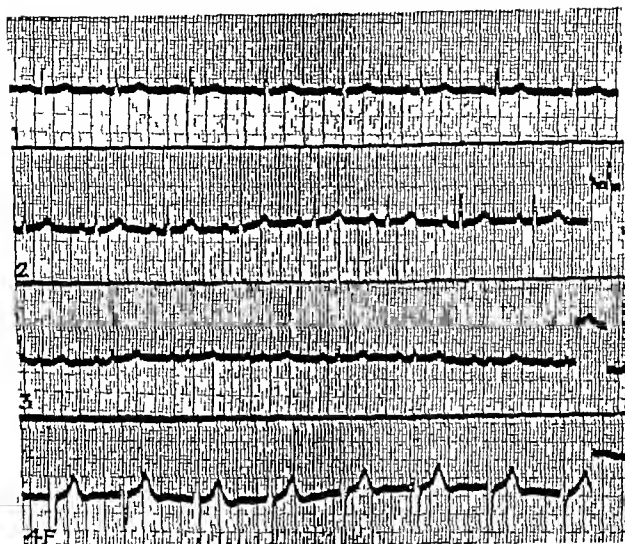


Fig. 17—Tracing made two days after cholecystectomy, showing return to a normal pattern for a man of 73 years

SUMMARY

1 Gallbladder disease and coronary artery disease (i.e., angina pectoris and acute coronary thrombosis) are frequently associated. Disturbances in cardiac rhythm frequently accompany gallstones

2. In properly selected cases, cholecystectomy frequently restores regular heart rhythm and at least ameliorates anginal pain

3 In experimental distention of the human gallbladder as recorded by the electrocardiograph we have observed changes in heart rate, disturbances in rhythm and conduction and some alteration of the T wave

CONCLUSION

Many of the fundamental problems in the gallbladder-heart relationship are still unsettled, and additional studies by detailed clinical observation, necropsy and experimental methods are needed. The operation of cholecystectomy in the human being affords an opportunity to make important physiologic observations. The individual practitioner can learn and add to our knowledge by careful observation and study of their patients with associated gallbladder and heart dis-

ease over their whole lifetime. Real knowledge and rich experience come from such lifetime observation of any disease process. At the same time we should remember that in nature probably nothing is simple. In dealing with biological phenomena the variables are infinite and if our explanation of any process is simple, it probably is not accurate. Our task as practitioners of medicine, dealing with human beings both in health and disease, obviously is not a simple one.

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THE ELECTROCARDIOGRAM IN AXIS SHIFT AND HEART STRAIN

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FOR many years we have been dissatisfied with the use of the term "axis deviation," since deviation in the direction of the QRS complex may occur in a number of different circumstances. It may be a normal event when the heart is shifted in its position because of the patient's habitus. It is produced by hypertrophy of the heart, by displacement of the heart, by block within the ventricles and by recent and old myocardial infarction. The distinction between these several circumstances cannot be derived from the deviation of QRS alone. For this purpose recourse must be made to the phases of QRS present in the several leads, to the final part of the ventricular complex, the S-T-T complex (which consists of the S-T junction, S-T segment and T wave) and to the appearance of the chest leads provided several of them are taken, viz., CF₂, CF₄ and CF₅. This information is then integrated with the clinical findings.

It is our belief that too much emphasis has been placed on the vector analysis of QRS in the limb leads in attempting to diagnose heart strain. We have found it a time-consuming procedure which does not repay the electrocardiographer for the information obtained. With increasing experience the importance of the various specific patterns in the electrocardiogram is becoming widely recognized.¹ In our department such specific patterns have been employed in the diagnosis of axis shift and heart strain.^{2, 3, 4} This is based on the appearance of the electrocardiogram in the three standard leads and the three chest leads mentioned above. The value and accuracy of these two patterns has been subjected to critical analysis with necropsy control over a period of years. These studies have revealed the value of criteria established for the diagnosis of these two patterns.^{5, 6}

The recognition of the electrocardiographic manifestations of heart strain permits this method to be utilized as a valuable supplement to physical and x-ray examination. It serves to help indicate that a stress has not yet produced definite heart strain or that it has already resulted in such heart strain. In fact, the electrocardiographic evidence

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often antedates other evidence. This specificity is very important in the evaluation of the clinical course of hypertension, acquired valvular lesions, coronary artery disease, coarctation of the aorta and other congenital malformations, emphysema and bronchial asthma, to mention a few. The presence of heart strain, of course, is evidence of a more advanced state of heart disease, i.e., a later period in the natural history of the disease.

The term "axis shift" is used to denote a normal alteration in the QRS direction due to a normal variation in the heart's position. Heart strain denotes abnormalities in the electrocardiogram due to strain (and consequent ventricular hypertrophy) of the right, left or both hearts. The term "heart strain" is preferred to that of "ventricular preponderance" because (1) It carries with it the idea that the heart muscle is strained to the point where there is abnormal alteration in the electrical record. (2) It connotes a dynamic concept in contrast with a purely static and anatomical one. (3) It suggests that other factors besides hypertrophy may contribute to the electrocardiographic contour without denying that hypertrophy is the primary factor involved.

In this discussion alterations in the direction of QRS associated with recent myocardial infarction, recent massive pulmonary embolism, or those found with block within the ventricles will not be considered, as such QRS alterations can be caused by these conditions per se and are therefore an integral part of these patterns.

AXIS SHIFT

Left Axis Shift—Left axis shift normally occurs when the cardiac apex is rotated to the left and upward, i.e., a "squat" heart. In the adult population about 20 per cent of all records will show left axis shift. Abnormal conditions which displace the heart to the right and at the same time cause a rotation of the heart on its long axis in a clockwise direction when viewed from its base may result in left axis shift. This may also occur during acute dilation of the left ventricle as in acute heart failure with similar rotation of the heart on its long axis. Thus, left axis shift may occur in abnormal as well as normal hearts. In fact it may be the only change noted in known cases of left heart strain. In children left axis shift is rarely a normal finding, the younger the child the more significant is the inversion of QRS in lead 3 as an indication of abnormality.

The criteria for diagnosing left axis shift are shown in Figure 18. The QRS duration is always normal (less than 0.11 of a second), the S-T-T segment is normal in appearance in the limb leads and the only unusual findings are a small upright QRS in lead 3 which is less than 2 mm, or an equiphasic or inverted QRS in this lead with a deep S wave, or the presence in lead 3 only of a deep Q wave between

one-fourth and one-half the size of R in the lead. The QRS complex in leads 1 and 2 are of normal size and contour. The chest leads, as shown in Figure 23, N, are normal in appearance. In brief, the diagnosis depends on the specific alterations in QRS in lead 3 outlined above when these occur without other abnormalities of the electrocardiographic configuration.

Left axis shift is to be differentiated from left heart strain and the variant with a deep Q_3 must be distinguished from coronary disease or an old healed myocardial infarct. While it is true that a deep Q_3 may be the sole residue of an old infarct, usually other stigmata re-

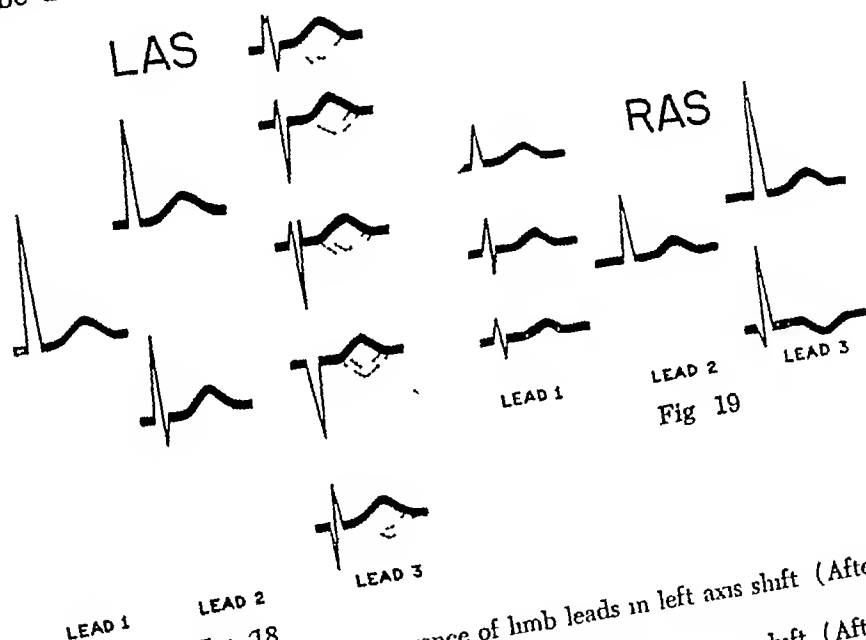


Fig 18 —Diagram of QRS appearance of limb leads in left axis shift (After Katz et al)⁵

Fig 19 —Diagram of QRS appearance of limb leads in right axis shift (After Katz et al)⁵

main also. Left axis shift with a deep Q_3 is usually encountered in pregnancy or obesity. As a rule, deep inspiration will abolish or markedly reduce the size of such a Q wave.

Right Axis Shift.—Right axis shift is a normal phenomenon and occurs when the cardiac apex is rotated to the right and downward, i.e., in a "pendulous" heart. In the older adult group seen by most cardiologists it is less common than left axis shift. The recent experience in screening young adults for the armed forces shows that it occurs with great frequency in the younger age group. Abnormal conditions which displace the heart to the left and at the same time cause a rotation on its long axis in a counter-clockwise direction when viewed

from its base may result in right axis shift. This may also occur during acute dilatation of the right ventricle as in acute right heart failure or following a major pulmonary embolus. The presence of right axis shift, although it is a normal variant in the electrocardiogram, may be produced by pathological conditions.

The criteria for the diagnosis of right axis shift are shown in Figure 19. The QRS duration is normal (less than 0.11 second). The S-T-T segment is normal in the limb leads and the QRS in leads 2 and 3 is also normal. Only in lead 1 are there significant changes in the QRS complex. The QRS in this lead may be small and upright, less than 2 mm, or equiphasic with a deep S wave. In this condition the chest leads are normal although a deep S wave may occur in CF_6 . Thus, the diagnosis depends upon the isolated findings of QRS changes in lead 1. The differentiation of right axis shift from a full-blown right heart strain is not difficult but some confusion may arise in less advanced stages of right heart strain. It should be recalled that on occasion a right axis shift may be the residue of an old anterior wall infarct but usually other stigmata will be present to orient the interpreter.

HEART STRAIN

Left Heart Strain—Left heart strain occurs when the strain and ventricular hypertrophy is predominantly in the left heart. The conditions which commonly lead to left heart strain are primarily hypertension, coronary artery disease, aortic valve regurgitation, aortic stenosis, pure and marked mitral valve regurgitation, and coarctation of the aorta. The fact that these conditions lead to left heart strain does not imply that every time they are diagnosed clinically the patient has significant left heart strain. It is one of the merits of electrocardiography that it helps to determine the development and progress of strain in the presence of these causes.

Four types of patterns, the first, second, mixed and concordant types, are encountered in left heart strain. They are based on the appearance of the limb leads. The chest leads in all forms are similar. In all types, the QRS is of normal duration.

In the first type (Fig. 20) the changes are confined in the limb leads to the QRS in leads 2 and 3. QRS is normal in lead 1 but is tall and the S-T-T in all the limb leads is normal in appearance. In lead 3, QRS is mainly or almost entirely inverted with a deep S wave. In lead 2, QRS is either upright and small (less than 2 mm), equiphasic with a deep S or mainly or almost entirely inverted with a deep S.

In the second type (Fig. 21) the QRS in lead 3 is similar to that seen in left axis shift except that the QRS is neither upright, nor has it a deep Q, in short, QRS is equiphasic or inverted with a deep S. Furthermore, QRS in leads 1 and 2 is normal although QRS in lead 1 is apt to be tall. The chief abnormality is in the S-T-T of leads 1 and 2.

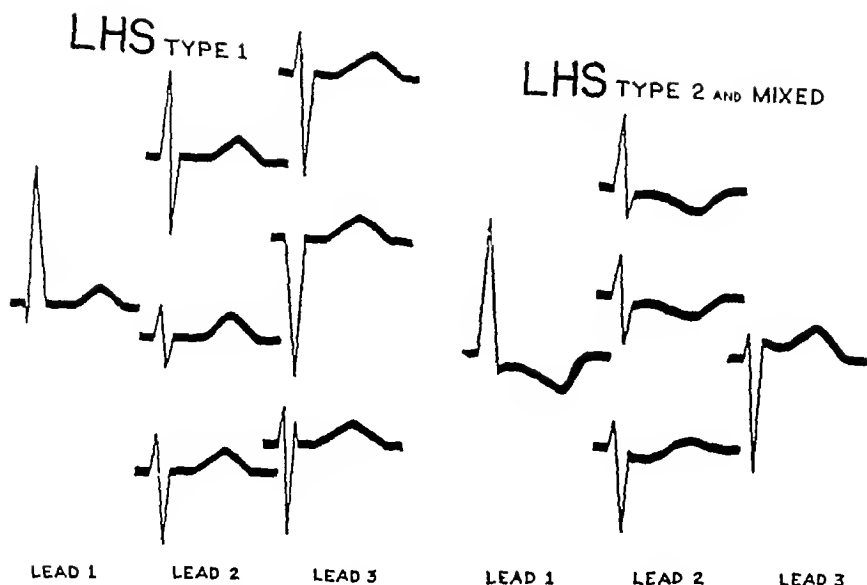


Fig 20.

Fig 21

Fig 20 —Diagram of QRST appearance of limb leads in first type of left heart strain (After Katz et al.)⁵

Fig 21 —Diagram of QRST appearance of limb leads in second and mixed types of left heart strain (After Katz et al.)⁵

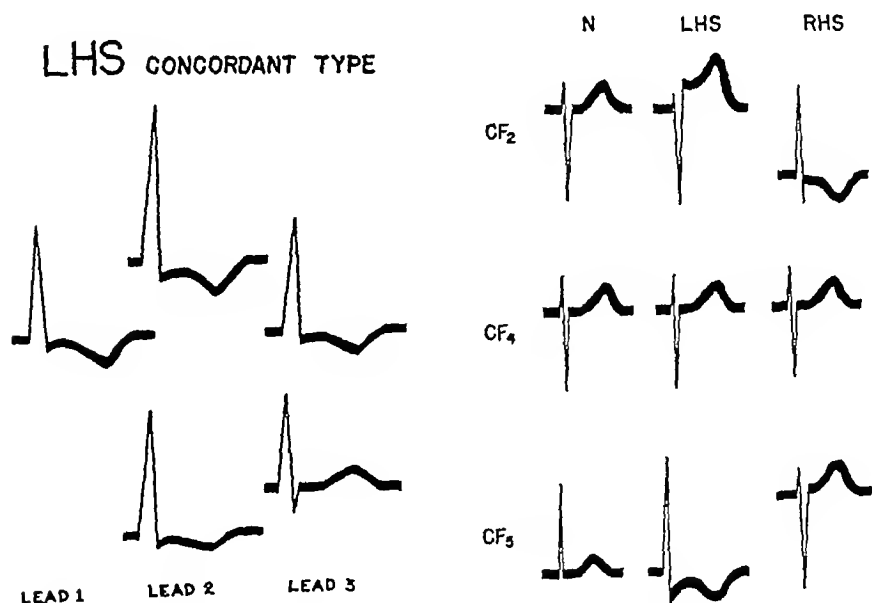


Fig. 22

Fig 23

Fig 22 —Diagram of QRST appearance of limb leads in concordant type of left heart strain (After Katz et al.)⁵

Fig. 23 —Diagram of QRST appearance of chest leads CF₂, CF₄ and CF₅ in normal (N), left (LHS) and right (RHS) heart strain (After Katz)⁷

or in lead 1 alone. This is what we have called the inverted S-T-T of heart strain, in it the S-T junction is abnormally depressed and so is the S-T segment which is bowed up and followed by an inverted asymmetrical T. A similar S-T-T configuration may be present in lead 2. In lead 3, the S-T-T may be the mirror image of that described for lead 1.

In the mixed type (Fig 21) there is a combination of the QRS changes seen in the first type and the S-T-T changes seen in the second type. The concordant type (Fig 22) occurs in about 15 per cent of cases of left heart strain. In this type the S-T-T configuration in leads 1 and 2 resemble that seen in the second type but the QRS is not inverted in any limb lead. It is upright in all of them.

Recent experience has been convincing that left heart strain may be more clearly revealed by analysis of the chest leads such as we employ than by the limb leads.⁴ In fact, the chest leads may actually show conclusive evidence when the limb leads are equivocal. The classical changes are shown in Figure 23 (LHS). They consist of the contrasting appearance of lead CF_2 and CF_6 . In CF_2 , the QRS is entirely or almost entirely inverted with an absent or abnormally small R, and S-T is elevated, often abnormally, and T is upright and tall. In CF_6 , the QRS is upright and tall with the S-T-T segment resembling that seen in lead 1 in the second type, viz., S-T is depressed and bowed up and T is inverted and asymmetrical. In CF_4 (or the apex lead) the changes are variable, CF_4 may resemble CF_2 or CF_6 , may be intermediate or may be normal.

The first type of heart strain should be differentiated from left axis shift. Ordinarily this is not difficult if the chest leads show the characteristics diagnostic for heart strain. Where the chest leads are equivocal the differential diagnosis may be influenced by the clinical findings.

The first type of left heart strain should not be diagnosed when there is a small upright QRS in lead 1. When such a small upright QRS in lead 1 is associated with a deep S wave in leads 2 and 3, three conditions should be thought of: (1) a combined strain of both hearts with neither one dominant—so-called combined heart strain, (2) a change in the position of the heart, or (3) the residue of an old anterior wall infarct. The differentiation between these three conditions is not easy and it may rest entirely on whether or not the chest leads show a left heart pattern, stigmata of an old anterior wall infarct or a normal configuration. This small R_1 with deep S_2 and S_3 should not be considered equivalent to the first type of left heart strain.

The second and mixed types of left heart strain are readily differentiated from coronary patterns, which they on occasion superficially resemble, by the difference in the configuration of the S-T-T segments. In heart strain the S-T deviation is in the same direction as the devi-

ation of the T, and the T wave is asymmetrical. In the coronary pattern the S-T deviation is in a direction opposite to that of T, and the T wave is symmetrical, peaked and has rounded shoulders. Unfortunately, when these patterns of S-T-T are not full-blown, difficulties with interpretation may arise. Such intermediate S-T-T configurations in heart strain are not only difficult to distinguish from coronary S-T-T patterns but from those showing intermediate digitalis effects and those of nonspecific origin. When the S-T-T configuration is not definite, recourse must be had to the chest leads. These may often assist in the differentiation.

It should be emphasized that unlike left axis shift, in no instance of uncomplicated left heart strain will a deep Q wave be seen in any of the limb or the three chest leads described above.

Right Heart Strain.—Right heart strain occurs when the strain and ventricular hypertrophy is predominantly in the right heart. The common clinical conditions which may lead to right heart strain are mitral stenosis, chronic cor pulmonale whether due to chest deformities, emphysema or other pulmonary disease associated with pulmonary arterial hypertension, and congenital heart disease especially when associated with pulmonary atresia or stenosis, interauricular septal defects or overriding of the aorta. As in left heart strain, right heart strain may appear electrocardiographically before it is revealed by any other method of examination. In fact, the clinical distinction can be made on this basis between pulmonary disease and chest deformities, on the one hand, and the chronic cor pulmonale which they may produce, on the other. For similar reasons a distinction should be made between acoustic valve deformities and congenital lesions and those which are dynamically sufficiently severe to have led to right heart strain. The presence of right heart strain is evidence of a more advanced state of the disease.

The pattern seen in right heart strain in the limb leads is illustrated in Figure 24. The QRS duration is normal, less than 0.11 of a second. A diagnostic combination which per se indicates right heart strain is the occurrence of an inverted QRS in lead 1 with a deep S wave, which is associated with a QRS in lead 2 that is tiny and upright, that is equiphasic with a deep S wave, or that is mainly inverted with a deep S wave. QRS in lead 3 is upright and tall and sometimes a small Q_3 and, less commonly, a deep Q_3 occurs. This diagnosis is fortified when the inverted heart strain S-T-T pattern is seen in lead 3 or in leads 2 and 3. Less full-blown forms of the S-T-T pattern do occur in leads 2 and 3 but are found less often and hence are less valuable in the diagnosis of right heart strain than the S-T-T pattern is in left heart strain.

The chest leads in right heart strain are occasionally helpful (see Fig. 23, RHS). Two types of changes are encountered. The first is the

appearance of the inverted form of heart strain S-T-T in CF_2 . Since normally the S-T may be elevated as much as 2.5 mm, the S-T depression in CF_2 is less commonly seen in right heart strain than is T inversion in this lead. In the younger age group of adults and in children, care must be taken not to consider the normal T inversion in CF_2 as evidence of right heart strain. The second form of change found in the chest leads is far more important and may be considered pathognomonic. Normally the R wave increases in height when shifting the chest electrode from the left border of the sternum to the left anterior axillary line, at the same time the S wave becomes smaller. Thus the ratio R/S, that is, the height of R divided by the height of S, becomes larger as the electrode is moved laterally. When the R/S in CF_3 is smaller than the R/S in CF_2 , that is, the R/S ratio is the reverse of normal, then this is clear evidence of right heart

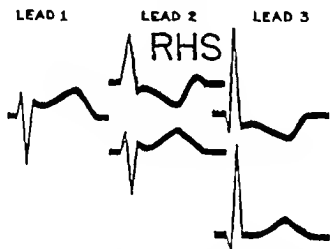


Fig. 24.—Diagram of QRS appearance of limb leads in right heart strain. (After Katz et al.)⁸

strain.⁸ Unfortunately this combination of the reversal of the R/S ratio is not encountered too often. More often it will be found that QRS in the chest leads is mainly or almost entirely inverted with deep S waves. Occasionally QRS in CF_2 may be upright, W shaped or polyphasic at the same time the QRS is deeply inverted in CF_3 .

Of added help in the diagnosis of right heart strain is the configuration of the P wave. The presence of a *P-mitrale* or a *P-pulmonale* pattern favors the diagnosis of right heart strain in a record which might otherwise be called right axis shift. The *P-mitrale* is found classically in cases of rheumatic mitral stenosis and consists of broad notched P waves in the limb leads. The *P-pulmonale* is found characteristically in cases of chronic cor pulmonale and consists of narrow and non-notched P waves which are small in lead 1, tall and peaked in leads 2 and 3 and inverted in the chest leads. Auricular fibrillation and flutter carry the same connotation as the P patterns mentioned above.

ation of the T, and the T wave is asymmetrical. In the coronary pattern the S-T deviation is in a direction opposite to that of T, and the T wave is symmetrical, peaked and has rounded shoulders. Unfortunately, when these patterns of S-T-T are not full-blown, difficulties with interpretation may arise. Such intermediate S-T-T configurations in heart strain are not only difficult to distinguish from coronary S-T-T patterns but from those showing intermediate digitalis effects and those of nonspecific origin. When the S-T-T configuration is not definite, recourse must be had to the chest leads. These may often assist in the differentiation.

It should be emphasized that unlike left axis shift, in no instance of uncomplicated left heart strain will a deep Q wave be seen in any of the limb or the three chest leads described above.

Right Heart Strain.—Right heart strain occurs when the strain and ventricular hypertrophy is predominantly in the right heart. The common clinical conditions which may lead to right heart strain are mitral stenosis, chronic cor pulmonale whether due to chest deformities, emphysema or other pulmonary disease associated with pulmonary arterial hypertension, and congenital heart disease especially when associated with pulmonary atresia or stenosis, interauricular septal defects or overriding of the aorta. As in left heart strain, right heart strain may appear electrocardiographically before it is revealed by any other method of examination. In fact, the clinical distinction can be made on this basis between pulmonary disease and chest deformities, on the one hand, and the chronic cor pulmonale which they may produce, on the other. For similar reasons a distinction should be made between acoustic valve deformities and congenital lesions and those which are dynamically sufficiently severe to have led to right heart strain. The presence of right heart strain is evidence of a more advanced state of the disease.

The pattern seen in right heart strain in the limb leads is illustrated in Figure 24. The QRS duration is normal, less than 0.11 of a second. A diagnostic combination which per se indicates right heart strain is the occurrence of an inverted QRS in lead 1 with a deep S wave, which is associated with a QRS in lead 2 that is tiny and upright, that is equiphasic with a deep S wave, or that is mainly inverted with a deep S wave. QRS in lead 3 is upright and tall and sometimes a small Q₃ and, less commonly, a deep Q₃ occurs. This diagnosis is fortified when the inverted heart strain S-T-T pattern is seen in lead 3 or in leads 2 and 3. Less full-blown forms of the S-T-T pattern do occur in leads 2 and 3 but are found less often and hence are less valuable in the diagnosis of right heart strain than the S-T-T pattern is in left heart strain.

The chest leads in right heart strain are occasionally helpful (see Fig. 23, RHS). Two types of changes are encountered. The first is the

appearance of the inverted form of heart strain S-T-T in CF_2 . Since normally the S-T may be elevated as much as 2.5 mm., the S-T depression in CF_2 is less commonly seen in right heart strain than is T inversion in this lead. In the younger age group of adults and in children, care must be taken not to consider the normal T inversion in CF_2 as evidence of right heart strain. The second form of change found in the chest leads is far more important and may be considered pathognomonic. Normally the R wave increases in height when shifting the chest electrode from the left border of the sternum to the left anterior axillary line, at the same time the S wave becomes smaller. Thus the ratio R/S, that is, the height of R divided by the height of S, becomes larger as the electrode is moved laterally. When the R/S in CF_5 is smaller than the R/S in CF_2 , that is, the R/S ratio is the reverse of normal, then this is clear evidence of right heart

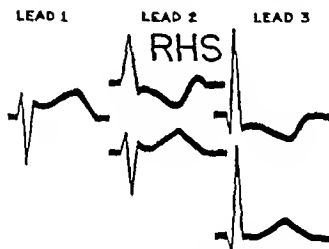


Fig 24.—Diagram of QRS appearance of limb leads in right heart strain. (After Katz et al)⁸

strain.⁸ Unfortunately this combination of the reversal of the R/S ratio is not encountered too often. More often it will be found that QRS in the chest leads is mainly or almost entirely inverted with deep S waves. Occasionally QRS in CF_2 may be upright, W shaped or polyphasic at the same time the QRS is deeply inverted in CF_5 .

Of added help in the diagnosis of right heart strain is the configuration of the P wave. The presence of a *P-mitralis* or a *P-pulmonalis* pattern favors the diagnosis of right heart strain in a record which might otherwise be called right axis shift. The *P-mitralis* is found classically in cases of rheumatic mitral stenosis and consists of broad notched P waves in the limb leads. The *P-pulmonalis* is found characteristically in cases of chronic cor pulmonale and consists of narrow and non notched P waves which are small in lead 1, tall and peaked in leads 2 and 3 and inverted in the chest leads. Auricular fibrillation and flutter carry the same connotation as the P patterns mentioned above.

The implication is that the P patterns and the fibrillation or flutter of the auricles are evidence of auricular damage and therefore, presumably, the changes which might otherwise be called right axis shift are indicative of right heart strain.

The differential diagnosis of right heart strain when the pattern is full-blown is as easy as that of left heart strain. Many times, however, doubt may remain in the differentiation from extreme right axis shift. We have been undergoing a considerable revision in our ideas about the diagnosis of right heart strain and are at present demanding much more evidence than formerly before making this diagnosis in the electrocardiogram.

Combined Heart Strain.—Combined heart strain occurs when the strain and ventricular hypertrophy is marked but not definitely predominant in either heart. Since the most frequent cause of right heart strain is left heart strain, the incidence of combined heart strain is higher than might be appreciated. Until recently it has been assumed that when heart strain is present in both the right and left hearts, the electrocardiogram will manifest one or other of these patterns. Recently it has become clear that often features of right heart strain will be combined in a single record with features of left heart strain. This is the basis of the concept of combined heart strain. It is as important as the recognition of the special S-T-T patterns encountered in heart strain in our concept of heart strain. These considerations place the electrocardiogram on a far more utilitarian plane than the over-concentration so prevalent in the past and still widely practiced at the present time in emphasizing only the vector analysis of the QRS complex in the diagnosis of heart strain. The presentation of these varieties of combined heart strain is too complex and requires more space than is at our disposal in this report. The reader is referred to previous publications from this department for details^{3,7}

CONCLUDING REMARKS

In this presentation we have attempted to depict the manner of approach which we have practiced in studying the configuration of the electrocardiogram. So much has been written on the coronary contour that there has been a tendency to consider this whenever abnormalities in the electrocardiographic pattern are encountered. This has led to an improper utilization of the electrocardiogram for one of its really valuable purposes, namely, the recognition of strain upon the heart. This has been abetted by the concentration upon QRS direction regardless of cause as exemplified by the widespread utilization of the term "axis deviation." This concentration upon vector analysis of the QRS complex, with failure to consider adequately the contour of the S-T-T segment and to evaluate the appearance of the chest leads, has been responsible for the lack of utilization of the

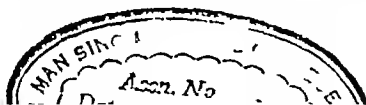
electrocardiogram in determining the presence, location and degree of heart strain in patients

It was the dissatisfaction with the traditional method of approach that led us to study the appearance of the ventricular complex in the six leads which we employ, to evolve specific patterns for the various types of heart strain and to distinguish them from normal displacements of the heart and from other conditions which can be recognized in the electrocardiogram which, incidentally, alter the direction of QRS. These patterns which we have described in this communication have been checked against the clinical course, and the x-ray configuration, and have been compared with necropsy findings. We have found them remarkably accurate and of practical value, provided that these patterns are called only when the combination of findings are definite and clear.

The only hazard with this approach to electrocardiographic evaluation is the temptation to describe an electrocardiogram as showing a definite pattern when the findings are not complete. This is especially prone to be the case when the record is read by the uninitiated, by the overzealous and by the clinician who looks in the electrocardiogram for corroboration of a clinical hunch. The electrocardiogram should be read objectively and independently of the rest of the examination if its value is to be utilized to the full. Only after judgment has been made in this way should it be integrated with the other clinical findings and the interpretation reviewed.

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SOME PROBLEMS IN THE DIAGNOSIS OF CHRONIC BRUCELLOSIS

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CHRONIC brucellosis has been called a dreary and deceptive disease.¹ The clinical picture frequently is characterized by a multiplicity of vague and shifting complaints, so that, often as not, the patient is stigmatized as a psychoneurotic. One author² has listed 150 symptoms and manifestations observed in patients with chronic brucellosis. Localizing infections have been described for virtually every organ and system in the body. Osler's well-known aphorism, "Know ye syphilis in all its manifestations and relations and all things clinical will be added unto you," could readily be said of brucellosis.

It frequently has been said that the diagnosis of a disease is easy once the possibility of its presence occurs to the physician. Would that this were true of brucellosis! There are no pathognomonic signs or symptoms of the chronic disease. Add to this the fact that we have no completely reliable and satisfactory laboratory procedure for its detection, and one need not wonder why there is so much confusion surrounding its diagnosis. The disease not only is frequently overlooked, but the opposite error is at times committed—overenthusiasm leading the unwary into making the diagnosis too readily on the basis of inadequate data. Other important diseases may thereby be overlooked. It has been said that no other disease is known in which the diagnosis requires a saner clinical judgment,³ and the ability of the best of physicians may be taxed.

Definite criteria are not established for the diagnosis of brucellosis, except for the isolation of the causative organism from the blood or other tissues. Unfortunately, this is seldom possible in chronic infections. Sound diagnosis, therefore, must be based upon an investigation and correlation of many aspects of the case, and upon a well-balanced evaluation of the entire clinical picture. It is a mistake to lean too heavily on laboratory procedures, and particularly upon any one test. A ready knowledge of the limitations, the sources of error, and the valid interpretations of the various tests employed is essential. The considerations of importance in arriving at a diagnosis of chronic brucellosis are presented in Table 1.

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TABLE I —FACTORS TO CONSIDER IN THE DIAGNOSIS OF CHRONIC BRUCELLOSIS

- I. Symptoms and clinical course
- II. Physical signs
- III. Epidemiology
- IV. Laboratory procedures
 - A Tests specific for brucellosis
 - 1 Isolation of brucella from the patient by culture and/or animal inoculation
 - a Blood
 - (1) Venous blood
 - (2) Arterial blood after splenic contraction by epinephrine
 - b Lymph nodes
 - (1) Biopsy
 - (2) Aspiration
 - c. Sternal marrow aspiration
 - d. Surgical specimens
 - e Urine
 - f Feces
 - g Other body excretions in suitable cases
 - 2. The agglutination test
 - 3 The opsonocytophagic test (opsonic index)
 - 4. Intradermal tests
 - B General tests which may be of value
 - 1 Blood counts (especially leukocyte and differential counts)
 - 2 Erythrocyte sedimentation rate

SYMPTOMS AND CLINICAL COURSE

In a discussion of chronic brucellosis, consideration must also be given the acute form of the disease, for in a malady which runs such a variable course, both as to severity and duration, no sharp division exists between the acute and chronic phases. Spink¹ divides his cases entirely on the basis of duration and more or less arbitrarily defines brucellosis as chronic if the patient has manifestations of the disease for three months or longer. Many physicians consider severity of symptoms as important as the duration in classifying the infection. At times a patient with an initially severe illness marked by high fever, sweats and prostration subsequently develops a persistent debilitating illness, lasting for months or years. On occasion, the reverse situation may be true. However, the great majority of the chronically ill patients do not recall a preceding acute illness, nor do they experience severe exacerbations. Simpson² has estimated that less than 10 per cent of the patients with chronic brucellosis have experienced a previous acute febrile illness compatible with a diagnosis of the acute disease.

Acute brucellosis usually presents a clinical picture suggestive enough to warrant a provisional diagnosis without the aid of the laboratory, and usually it is as readily diagnosed as most acute febrile illnesses. After a prodromal period, often prolonged, there may be an insidious onset, or a sharp chill may initiate a stormy period marked

by repeated rigors, high fever often reaching 103° to 105° F. in the evening but becoming normal or subnormal in the morning, drenching sweats, extreme prostration, occipital headache, intense backache, generalized muscle and joint pains, anorexia, weight loss, and abdominal pain which may simulate a surgical abdomen. Insomnia, restlessness and a coarse tremor frequently accompany the fever. It is in this stage of the disease that brucella organisms can usually be cultured from the blood if persistent efforts are made.

Chronic brucellosis presents quite a different situation. Without pathognomonic symptoms, often without any physical signs, with a remarkably great variety and diversity of manifestations, and frequently with equivocal laboratory tests, the physician may be hard put to make a definite diagnosis even after a prolonged study with full use of all laboratory facilities. He may be unable to find objective evidence to establish the diagnosis, but neither can he say that the patient does not have the disease. It is natural enough under such circumstances that on the one hand some physicians are skeptical of the whole problem of chronic brucellosis and entertain doubts as to its widespread prevalence, while on the other hand the enthusiast diagnoses and treats as brucellosis every vague complainer that comes into his office.

Although scores of symptoms may be present, the following features are most commonly encountered. A multiplicity of obscure and shifting complaints is a distinguishing mark, and in this respect the resemblance to the psychoneuroses is conspicuous. If any one symptom can be said to occur with regularity, it is fatigue. Fatigue and weakness, although present at rest, are most troublesome when attempts are made to perform even a slight amount of work of the lightest sort. This everlasting weariness may be the only complaint, and one sometimes suspects a degree of malingering for the secondary gains. Many times the patient simply states that he just does not feel well and can offer no further explanation. Persistent low backache may be a most troublesome symptom, and no objective signs can be found to explain it. A succession of indefinite aches and pains in the muscles, joints, bones and nerves may plague the sufferer. Low grade fever is present, often for months at a time, but again it may be absent for long periods while other symptoms persist. True chills are infrequent in the chronic phase of the illness, but chilly sensations even in warm weather are prevalent. Vague abdominal distress, the character of which usually suggests a functional origin, may at times become severe enough to simulate an acute surgical abdomen.⁴ Anorexia with its resultant weight loss is almost constant. Constipation is the rule, diarrhea almost never being a part of the picture. Symptoms referable to the nervous system and to the emotions are notorious. The patient is discouraged, defeated and depressed. At times he is irritable, rest-

less, and apprehensive, and he weeps at slight or no provocation. Insomnia may become habitual. Tremors, especially of the lips, may be present. Headaches may be most annoying and persistent.

Although the sufferer may be a chronic invalid, partially or totally incapacitated for months or years at a time, many patients carry low grade infections and experience but little difficulty for long periods. They lead productive lives interrupted by occasional bouts of fever and symptoms of a few days or weeks duration. Seldom, however, does the victim appear to be in robust health.

CASE I.—G F, a 40 year old white man, a carpenter, was seen in the Orthopedic Clinic on April 3, 1945 complaining of a persistent low back pain of fifteen months duration. The onset occurred a few days after a minor injury suffered when he backed into a post while in a stooping position. Roentgenograms made on December 30, 1943 showed a fracture of the coccyx, subsequent films on March 30, 1944 indicated healing with a good union. Nevertheless, pain in the lower lumbar region continued persistently thereafter. At no time was it very severe nor did it interfere materially with his work. Physical examination was noncontributory and the routine blood counts, urinalysis and serology were normal. The examining physician recorded his impression as follows: "Normal healthy male with functional bowel distress background and knack for exaggerating small, unimportant symptoms."

A brucella agglutinin survey was then being made on discarded Wassermann sera. His test was positive in a dilution of 1:500 (the highest titer of the method used).

Reexamination in the Medical Clinic with this finding in mind provided the following additional information. In December 1944 (one year after the onset of back pain) he suffered an attack of "flu" which confined him to bed for about a week. He had fever and "ached all over." Aside from this and his persistent low grade backache he felt that he had been in good health for many years. He denied any other fever, or any sweats or chills. For several years, however, he had noted chilly sensations on going outdoors. He denied any unusual fatigue or weakness. He slept well and he declared that he was not nervous except for a "nervous stomach" which had been present for years. His appetite was good, and he did not suffer from constipation, headache, cough or rheumatism.

Physical examination was not remarkable except for some questionable generalized abdominal tenderness and for small shotty lymph nodes palpable bilaterally in the epitrochlear, axillary and inguinal regions.

At the second visit on April 24, 1945 a blood culture was made which was positive for *Br. abortus*. Another culture on May 17, 1945 was also positive. He was then treated with sulfamerazine for twenty two days: the blood levels ranging from 13.5 mg to 7 mg per 100 cc. Thereafter, all blood cultures have remained sterile (eight times during the ensuing twelve months). The backache, however, persisted for another two months and thereafter it has been present intermittently.

Other pertinent laboratory examinations were as follows: Ten agglutination tests ranged from as high as 1:2560 in May 1945 to 1:160 one year later. Several opsonocytophagic tests showed an infection picture with slight to moderate phagocytosis predominating. This test gradually improved so that, one year later, it indicated a fairly good immune response (80 per cent marked phagocytosis). Seven erythrocyte sedimentation rates were completely normal, ranging from 2 to 5 mm per hour (Wintrobe). Eleven leukocyte counts during the year's observation ranged from 2900 to 7550 per cu. mm., only three counts being as high as 5000. A relative lymphocytosis was observed on several occasions.

This patient had lived in suburban Chicago all of his life and he regularly

drank pasteurized milk. He had never lived in a rural area or worked on a farm or in the meat-packing industry. Several times a year he went on hunting and fishing trips. He recalls that in September, 1945 (three months before the onset of his backache) while on a hunting trip in South Dakota, he drank raw milk at a farm where several of the cows were sick, one of them dying the following day. Five of his companions who also drank the milk have remained well.

Comment—Although suffering from undoubted chronic brucellosis, proved by two positive blood cultures, this man experienced relatively little inconvenience. Except for the one-week attack of "flu," which likely was an acute exacerbation of the brucellosis, he had worked at his trade steadily. His persistent low grade and nonincapacitating backache was his only real complaint. On direct questioning, he repeatedly disclaimed any of the symptoms commonly associated with this infection. In addition to the positive blood cultures, the activity of his infection was reflected in the strongly positive agglutination tests and the opsonic indices showing an infection picture. The marked change toward immunity which both of these tests showed during the following year further indicate the activity of the disease at the time of his initial examination.

Chronic localizing brucellosis may occur in conjunction with the generalized illness or independently. Localization has long been recognized as a characteristic of brucella infections in animals, so it is not surprising to find its counterpart in the human. Lymph nodes are a favorite site. When the peripheral nodes are involved, the organism may be cultured from a biopsy or aspiration of the node, thereby providing a positive diagnosis in what may be an otherwise difficult case. Almost any organ of the body may be the site of a localized infection. Brucella have been recovered from tonsils, sinuses, alveolar abscesses, bones, joints, bursae, the spleen, the liver, the gallbladder, the colon, pleural effusions, ovarian cysts, uterine discharges and prostatic fluid. Orchitis, mastitis, cystitis, nephritis, meningoencephalitis, uveitis and a variety of cutaneous lesions have been attributed to it.

Ocular brucellosis is being more frequently recognized and probably accounts for a small proportion of that large group of infectious eye lesions of undetermined etiology. Woods and Guyton⁵ investigated 200 patients with endogenous uveitis and classified fifteen as "probably" due to brucellosis. Krause⁶ has seen ten cases of anterior or posterior uveitis attributed to brucellosis. Green⁷ and Burky and co-workers⁸ have also considered ocular brucellosis to be a frequently unrecognized disease.

Osteomyelitis both with and without arthritis has been described in many bones. The vertebral bodies, particularly in the lumbar region, are one of the commonest sites and here it may closely simulate

Pott's disease in many respects Psoas abscess formation may follow I have observed two patients with spondylitis probably due to brucellosis

CASE II—A. G., a forty-eight year old white woman, was first seen here on February 17, 1944. She recalled that three years before, she had suffered intense fatigue, profuse night sweats, a 20 pound weight loss, and afternoon fever to 100° F. This had followed a vacation on a relative's farm in Michigan where she drank raw milk. These symptoms continued for nine months, during the latter part



Fig. 25 (Case II, A. G.)—Brucellosis of the lumbar vertebrae. The third lumbar is totally collapsed, with lesser involvement of the fourth lumbar. Large arrow indicates a fracture in one of the tibial bone grafts but functionally the spine was well stabilized. The five small arrows anterior to the spine indicate a soft tissue swelling which appeared postoperatively. The possibility of psoas abscess was considered but the area remained stationary for sixteen months and probably resulted from a bulging of soft tissues compensating for the collapsed vertebra.

of which period she had received intradermal brucella vaccine therapy. Thereafter she was relatively free from symptoms except for recurrent skin lesions on the legs closely resembling erythema nodosum. Recurrent corneal ulcers also appeared during this period. In October and December 1943 she again suffered febrile illnesses initiated by sharp chills and marked by fever persisting eighteen days in October and seven days in December. Fatigue, night sweats, nausea, vomiting and nervousness accompanied these attacks.

A febrile illness recurred again in May 1944 at which time she was admitted to Billings Hospital. In this episode her fever persisted for seven weeks and finally fell by lysis. During the first three weeks it reached daily peaks of 104° to 106° F. generally becoming normal or subnormal in the mornings. Frequent chills drench-

ing sweats, extreme prostration, backache, headache, nausea and vomiting were prominent symptoms. The spleen was questionably enlarged. The agglutinin titer during this period varied between 1:640 and 1:1280 and the opsonic index was characteristic of infection. Many venous blood cultures were made but no organisms were recovered. She was extremely sensitive to the brucellergin skin test. Acute symptoms subsided gradually, but during the ensuing year she continued to be an invalid with numerous complaints.

Pain in the lumbosacral region eventually became her major symptom and it became so severe that she was readmitted to the hospital on March 4, 1945. Roentgenograms of the lumbosacral region made previously (March, 1944) had shown a normal spine. New films in March, 1945 revealed grossly destructive lesions of portions of the bodies of the fourth and fifth lumbar vertebrae. The appearance was typical of that seen in tuberculosis of the spine but chest films, pyelograms and tuberculin skin tests disclosed no evidence suggesting the presence of an acid-fast infection. The temperature record remained essentially normal during this hospitalization. Brucella agglutinin titers were 1:320 and the opsonic index showed a moderate immunity. With the patient at bed rest in the hospital the back pain continued to be intolerable, serial x-rays showed some progression of the lesion, and a gibbus appeared. On April 18, 1945 a spinal fusion operation was performed using tibial bone grafts.

Surgical recovery was uneventful and roentgenologic progression of the lesion ceased (Fig 25), but the patient remained in the hospital for another six months, afebrile and objectively doing well but complaining of many things, chiefly of unbearable pain in the back and the lower extremities. She constantly demanded sedatives and analgesics. No material cause for the severity of her symptoms could be found in spite of a persistent search. She insisted that she was unable to get out of bed and refused to make serious attempts to walk, despite strong encouragement and repeated offers of help. Because she habitually lay on her side with the knees drawn up, notwithstanding frequent admonitions to lie straight, flexure contractures developed in the hips and knees. Little improvement could be noted following the administration of daily physiotherapy, including inductotherm, massage, warm pool, and walking training. In October, 1945 she was discharged to the care of a relative, still essentially a bedridden invalid.

The patient was not seen again until May, 1946, at which time she was again admitted to the hospital in much the same condition as at the time of discharge seven months before. Daily physiotherapy during this three-month hospitalization produced considerable improvement. The contractures were largely eradicated, she could again stand fairly erect, and she began to walk with the aid of crutches. She also swam and floated in the warm pool. Her pain and general complaints largely subsided.

Many physicians who saw her during the period following her spinal fusion operation expressed the opinion that large elements of hysteria and perhaps of malingering were present, but a Minnesota Multiphasic Personality Inventory done July 9, 1946 showed no gross abnormality. The hysteria score of 63 was the highest one obtained for any of the schedules. This test, however, was made after much general improvement had taken place.

PHYSICAL SIGNS

Physical signs in chronic brucellosis usually are notable for their absence, and in the majority of patients, no signs attributable to the infection can be demonstrated. Enlargement of the spleen can be detected in but a few patients. Enlargement of lymph nodes occurs somewhat oftener. Abdominal tenderness is also worthy of mention.

Localizing infections with their appropriate signs should be sought during the complete physical examination which, of course, should be given to every patient suspected of having the disease

EPIDEMIOLOGY

An evaluation of the possibilities and probabilities of a patient having had an opportunity to acquire a brucella infection should be a part of the investigation of every suspected case. This presupposes some knowledge of how the disease is spread. The use of raw milk products from infected herds and direct contact with infected animals

TABLE 2.—EPIDEMIOLOGY OF HUMAN BRUCELLOSIS

- I. Animals to man through dairy products (gastrointestinal portal)
 - A. Unpasteurized products
 - 1 Milk
 - 2 Cream
 - 3 Buttermilk
 - 4 Butter
 - 5 Cheese
 - 6 Ice cream
 - B Improperly pasteurized products
- II. Animals to man by direct contact (cutaneous portal?)
 - A. Animals that harbor infection
 - 1 Cows
 - 2 Swine
 - 3 Goats
 - 4 Sheep
 - 5 Horses
 - 6 Dogs
 - 7 Fowls
 - B Occupational groups affected
 - 1 Farmers
 - 2 Dairymen
 - 3 Slaughter house workers
 - 4 Veterinarians
- III. Infections in laboratory workers
- IV Methods theoretically possible, but without evidence of their importance in natural transmission of the disease
 - A Man to man
 - B Mother's milk
 - C Insects
 - D Water
 - E Sparrows

account for the great majority of cases Table 2 summarizes the epidemiology of human brucellosis

Infections acquired from the use of unpasteurized dairy products probably surpass numerically those acquired by all other routes. Quite naturally the incidence of the disease is higher in rural regions. The

city dweller, however, is not exempt even though his city has the standard milk ordinance recommended by the United States Public Health Service and 100 per cent pasteurization of milk is enforced. In some cities where only pasteurized milk is legal, bootleg milk stations or "jug stations" operate just outside the corporate limits and thus outside the jurisdiction of city health officials.⁹ Such milk rarely is pasteurized and frequently comes from farms of such unsanitary condition that their product is not acceptable for sale in the city. The week-end in the country and the fishing or hunting trip account for many of the infections in the urban population. Whereas enlightened people refuse to touch raw milk, they may forget about the hazards of raw cream in their coffee, or may overlook the questionable source of ice cream. Raw cream may be a particularly hazardous product because the fat globules carry up the organisms when they rise to the surface.¹⁰ Infections have also been traced to unpasteurized cheese, both native and imported.

Studies on the viability of brucella indicate that ice cream¹¹ made from naturally infected milk and stored at 32° F may harbor viable organisms after thirty days. When butter was inoculated with *Br abortus* and stored at 46.4° F, organisms remained viable for 142 days.¹⁰ Roquefort cheese has harbored live *Br abortus* for two months.¹²

Unfortunately, many municipalities do not have ordinances requiring pasteurization and much raw milk is still sold even in fairly large cities. The hazards of unpasteurized milk may be appreciated when we consider that Graham and Torrey¹³ isolated brucella from 50 per cent of sixty-two raw milk samples taken from milk depot vats of pooled milk in twenty-eight widely scattered Illinois counties. Pasteurization as employed in five different types of pasteurizers effectively destroyed brucella in thirty-one samples of milk collected from the same sources. Defects in pasteurization equipment or technique might readily fail to kill all brucella, for the difference between the time and temperature requirements to kill some strains and that used in pasteurization practice is not great.¹⁴

Infections transmitted directly from animals to man by direct contact are of importance in certain occupational groups, notably farmers, dairymen, slaughter-house workers and veterinarians. When brucellosis is suspected in farmers or dairymen, specific inquiry should be made concerning the results of Bang's tests as well as the occurrence of suspicious symptoms in their herds. If a herd has not been Bang's tested, steps to this end should be initiated. The fact that a patient works for a meat-packing firm may be of slight significance, for he may be an office worker with little or no exposure. Inquiry should be made as to the specific nature of his work and especially as to the amount of contact with animals or with fresh-killed meat.

In this country animal brucellosis is most important in cows and swine, but in some areas sheep are becoming more commonly implicated. Although the infection does occur in horses (fistula of the withers or poll evil),^{12 15 16} and dogs,¹² these sources are relatively unimportant in human contagion. Fowls are readily infected experimentally and a few naturally-occurring epidemics in chickens have been reported,¹² but it is unlikely that widespread infection exists in domestic fowls.

Transmission from man to man has never been demonstrated, but some patients are known to excrete brucella in urine or feces for long periods. There is no reason why those giving nursing care to such patients may not become infected unless precautions are observed. Mastitis may occur in chronic brucellosis and it is conceivable that in rare instances a mother might infect her nursing infant, but it would seem that the situation would seldom arise in which breast feeding should be contraindicated.

Brucella infection has been transmitted experimentally by mosquitoes and biting flies, and monkeys have been infected by inhaling dust containing *Br. melitensis*.¹² No epidemiological data exist indicating that these methods are of importance in the natural transmission of the disease.

LABORATORY PROCEDURES

Tests Specific for Brucellosis.—The details of the technical procedures for the various laboratory tests have been adequately presented elsewhere and will not be discussed here.

1 *Isolation of the causative organism from the patient* is the only absolute means for the diagnosis of brucellosis. Unfortunately this positive solution is seldom possible during the chronic phase of the infection, but adequate attempts should never be neglected.

Suitable media, such as tryptose broth and a 10 per cent carbon dioxide atmosphere should be employed. Repeated attempts should be made to culture the organism from the venous blood and in obstinate cases the organism may occasionally be grown from arterial blood drawn five to fifteen minutes after splenic contraction by the subcutaneous injection of epinephrine. Culture of sternal marrow aspirations is a simple technic by which it may be possible to isolate the organism in some instances. When suitable lymph nodes are available culture and/or animal inoculation of material obtained by biopsy or aspiration should be done. The utility of lymph node culture is limited by the fact that most of the chronically ill patients do not have freshly hyperplastic peripheral nodes. In those in which lymphadenopathy is present, the nodes are often fibrosed and relatively inactive. In suspected cases, surgical specimens of all sorts such as gallbladders, appendices, sequestra, ovarian cysts, ganglia and sinus discharges should be bacteriologically examined whenever they are available. Organisms have been recovered from urine and feces in selected cases.

2. *The brucella agglutination test* is probably the most widely used of all diagnostic methods, and rightly so. The question frequently is

asked, "What constitutes a clinically significant agglutinin titer?" A definite numerical answer cannot be safely given. Many consider a titer of 1:80 in the presence of characteristic symptoms to be presumptive evidence for brucellosis, but one must hasten to add that so many exceptions will arise, both above and below this dilution, that the figure really is of very little practical help. Interpretation of the test in terms of active infection may be very difficult indeed, and one must take stock of a number of established facts.

(a) A not inconsiderable number of patients with proven brucellosis develop little or no agglutinin response throughout the course of their illness. This is especially true of the chronic infections. Huddleson¹⁷ reported that in 100 patients with brucellosis due to *Br. abortus*, twenty-nine had negative agglutination tests. Taylor and associates¹⁸ in France found that of 442 patients with positive blood cultures (95 per cent *Br. melitensis*, 5 per cent *Br. abortus*), thirty-nine, or 9 per cent, had agglutinins in titers less than 1:80. Castaneda and associates¹⁹ found that of 100 patients with positive blood cultures, twelve had negative agglutination tests. *Brucella abortus*, which is more commonly seen in the United States, is considered a much poorer stimulator of agglutinins than *Br. melitensis*, which accounted for 95 per cent of the cases in both Taylor's and Castaneda's series.

(b) A positive agglutination test does not necessarily mean active infection. This is sometimes true, even when the test is positive in high dilutions. I have observed a fifty-nine year old Italian man who has repeatedly had a brucella agglutinin titer of 1:5000 during the past two years. The original test was performed during a routine brucella agglutinin survey made on Wassermann sera, and this man's serology was done as part of a pre-employment examination. He consistently denies any and all symptoms and he insists that he has never had a sick day in his life. He states that during the forty-three years he has lived in the United States, he has taken only two bottles of medicine—milk of magnesia—and he didn't need them. He works daily at hard manual labor and boasts of his physical vigor. No significant physical signs have been demonstrated and several blood cultures have been sterile. The opsonocytophagic test has shown a marked immune response on several occasions.

Parker Dooley²⁰ in 1932 presented a revealing report on the significance of agglutinin titers in the blood of 263 boys living at a boarding school where raw milk from a brucella-infected herd had been consumed. The study was begun after two of the students developed acute brucellosis. Of the 263 boys examined 41 per cent developed agglutinins in titers ranging from 1:40 to 1:12,000. Fifteen boys had titers of 1:320 or higher. With the exception of the two original cases, none of the boys showed any clinical manifestations of active infection.

(c) In general, the higher the titer the greater is the likelihood that it is associated with active infection.

(d) An agglutination test which is positive in a low titer early in the course of the disease and which becomes progressively higher in subsequent tests speaks strongly for active infection.

(e) It has been reported^{21, 22} and frequently stated that sensitive individuals may develop moderate agglutinin titers following brucella skin tests with both vaccines and brucellergen, regardless of whether the test is positive or negative. Our own experience does not confirm this in regard to brucellergen, but it is wise to defer skin tests until all other tests are completed.

(f) *Brucella* agglutinins which have been present in the past may reappear as the result of a subsequent febrile illness, such as pneumonia or typhoid fever. This nonspecific reappearance of agglutinins is called an anamnestic reaction.

(g) In our laboratory²³ as well as in others¹ a significant divergence has been

noted in brucella agglutinin titers of the same serum when tested with different antigens. To study the extent of such variations, sera were collected from twenty-two individuals known to have moderate titers. Portions of each serum were sent to five other laboratories (two private clinical laboratories, two public health laboratories, and one veterinary laboratory) and each serum was also tested in our own laboratory with eleven different commercial agglutination antigens. Both the slow test tube and the rapid slide methods were used. In every one of the twenty-two serum specimens great variations in titers were reported from the five laboratories as well as with the various antigens. With the exception of three sera, all were recorded as negative by one or more laboratories, eleven being called negative two

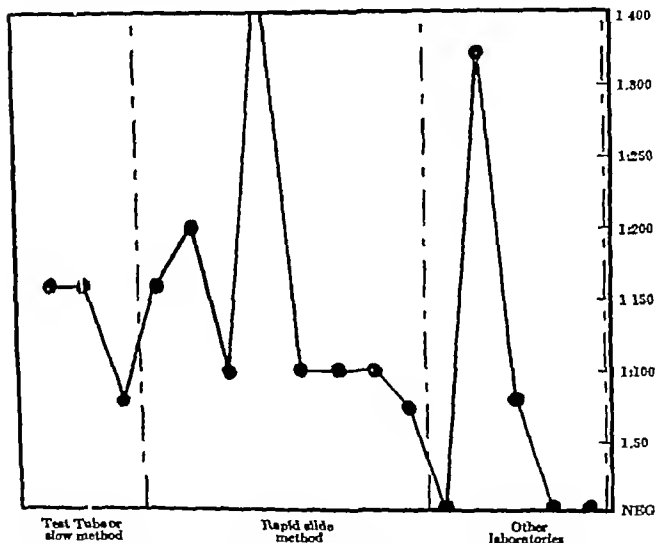


Fig 26.—A case of "probable" chronic brucellosis. Variations in titer of the brucella agglutination test performed on portions of the same serum with various commercial antigens and in different laboratories

or more times. Of the nineteen sera thus declared negative on one or more occasions, thirteen were elsewhere reported to be positive in dilutions as high as 1:320 and 1:640. Figure 26 presents a typical example of the fluctuations observed in one serum.

(h) Following the standard two-dose cholera vaccination, such as employed by the Army and Navy, about 90 per cent of the individuals so treated develop brucella agglutinins, often in titers as high as 1:320 or 1:640.²⁴ The opsonic index also becomes strongly positive.²⁵ This has been shown to be due to an H antigen common to the two organisms.²⁶ In some individuals titers persist for many months and possibly may reappear as an anamnestic response. Millions of veterans have

been vaccinated for cholera during their military service, and one can expect that further confusion will thus be introduced into the clinical interpretation of this test.

(†) It has long been known that tularemia may occasionally but not always stimulate brucella agglutinins, but the titer does not become high and is considerably lower than that developed for *Pasteurella tularensis*

3 *The opsonocytophagic test or opsonic index* is much less widely used than other tests for brucellosis, first because the procedure requires a precise technic involving the use of a smooth strain of living, virulent organisms and second, because controversy continues as to the validity and interpretation of the test.

The opsonic index is not suitable for a screening method. We have never found it to show appreciable phagocytosis in any individual with a completely negative agglutination test. As the name implies, this test measures the ability of the serum to stimulate the blood phagocytes to ingest living, virulent brucella organisms. Absence of phagocytosis indicates a noninfected, susceptible status whereas marked phagocytosis (60 to 100 per cent of the phagocytes containing forty or more organisms each) denotes an immune status. Intermediary tests suggest that either active infection is present or a former immune status is declining. We have found that when the test is performed carefully with precise technic and with frequent checking with known positive and negative control bloods, and when one does not attempt to interpret the test too closely, valuable information of two sorts may be obtained. First, it is a useful aid in deciding whether positive agglutination tests or skin tests indicate a present active infection or an immunity due to past contact with the organism. Second, when done serially in an actively infected subject, the opsonic index assists in following the progress of the disease. Because of the technical difficulties it would seem that this test would not be practical or reliable for use in the occasional case only.

4 Intradermal skin tests probably run a close second to the agglutination test in frequency of application, but they provide relatively little useful information and are commonly misused. Spink⁴ calls the intradermal test "the most abused diagnostic procedure." The test may be performed by injecting intradermally suitable amounts either of a nucleoprotein such as brucellergen, or of a bacterial vaccine. Keller,²⁷ testing seventy-six individuals known to have been allergic to brucella protein two years previously, found that tests made simultaneously with brucellergen and vaccine gave an almost identical number of positive results. Angle²⁸ in similar simultaneous tests found a somewhat greater number of positive reactors with vaccine than with brucellergen. Both authors, as well as others, have noted occasional cases in which tissue necrosis followed the intradermal vaccine but this has not been observed with brucellergen, therefore making this the more desirable antigen. The test should be read at forty-eight hours. Erythema which often appears early but fades before forty-eight hours have elapsed should not be regarded as a positive reading, a mistake not infrequently made. Edema of at least 0.5 cm diameter persisting at least forty-eight hours after the injection is the minimal requirement for a positive skin test.

Interpretation of the skin test should be quite analogous to that of the tuberculin test in tuberculosis. A positive reaction simply means exposure to brucella protein either currently or in the recent or remote past. The exposure may represent past or present clinical infection or repeated subclinical contact with brucella. It is conceivable that a positive skin test might follow the repeated ingestion of pasteurized milk containing exceptionally large numbers of killed organisms. No correlation exists between the degree of reaction and either the presence or the severity of active infection. As with the agglutination test, the skin test may remain negative throughout the course of an infection with bacteremia,²⁹ but this occurrence is not frequent. Large segments of the population have been reported to have positive skin tests. Spink and his associates¹ skin-tested 533 consecutive patients, largely from rural areas, who attended the Medical Out-Patient Clinic of the University of Minnesota Hospitals. Positive tests were obtained in 104, or 19.5 per cent. Of the positive reactors 85 per cent lived on a farm or rural area or consumed raw milk. Angle and coworkers²⁸ tested 7122 school children in Kansas City, Kansas. Positive reactions were found in 9 per cent of the entire group. As is the case with the tuberculin test, increasing percentages of positive skin reactions were observed in successive age groups. Of the positive reactors, 80 per cent consumed raw milk.

General Laboratory Tests Which May Aid in the Diagnosis of Brucellosis—1. *Blood counts* A moderate hypochromic anemia may occur in chronic brucellosis, but it is not characteristic and more often the hemoglobin and erythrocyte count remain quite normal.

Leukopenia with a relative lymphocytosis is frequently observed in brucellosis, especially in the acute phase, but normal counts or even moderate leukocytosis occur somewhat more often. Castaneda and Guerrero³⁰ studied the leukocyte picture in 888 random cases of brucellosis. Nearly a third of the cases showed moderate leukopenias with significant reduction of the polymorphonuclear leukocytes. About one-fifth of the cases exhibited a moderate leukocytosis. Munger and Huddleson³¹ observed ten cases of acute brucellosis on the Island of Malta. In four, the total leukocyte count was below 4000 and only one had a count greater than 5000. "Pathologic lymphocytes" or "large mature lymphocytes" resembling those seen in acute infectious mononucleosis were observed in 40 per cent of their cases.

2. *The erythrocyte sedimentation rate* may remain normal throughout the course of brucellosis, although moderate to marked elevations are more commonly seen. This is one of the few severe infections in which normal sedimentation rates are observed, and such an occurrence should lead one to consider the possibility of this disease.

CONCLUSIONS

The diagnosis of chronic brucellosis in many instances is a most difficult task requiring a sound clinical judgment. Suitable criteria may not be available to establish the diagnosis unconditionally, yet it may not be ruled out entirely. Undoubtedly the diagnosis is frequently overlooked, but perhaps equally often, patients with other infections or with psychoneuroses are labeled as victims of brucellosis.

inadequate or misinterpreted data. All aspects of the entire clinical picture must be investigated and evaluated. Although the laboratory may be most useful, seldom does it provide the whole answer. Even after prolonged study, the diagnosis often must remain "probable" brucellosis. In this disease laboratory data are especially apt to be misconstrued unless there is full recognition of the limitations, sources of error, and valid interpretations of the tests used.

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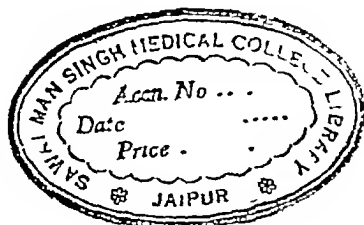
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SUBACUTE AND ACUTE DISSEMINATED LUPUS ERYTHEMATODES

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THE term "lupus erythematoses"‡ is a misnomer§ and is only historically justifiable. This poor name probably will not be changed until the causative agent of this disease is discovered. According to the original concept of Cazenave, who coined the name in 1851, it meant that the disease is an erythematous form of voracious "lupus" which in turn later proved to be a form of cutaneous tuberculosis. It is interesting to follow in the literature up to the past decade of this century the sometimes frantic efforts to prove the tuberculous etiology of this disease. One has the impression that often the driving force behind these attempts was the impressive name "lupus." In any case, all the "evidence" presented in favor of the tuberculous etiology has proved to be erroneous, and today the great majority of investigators agree that lupus erythematoses is a disease entity having no connection whatsoever with the tubercle bacillus.

The chronic form of this disease was ably discussed in this publication by A. W. Stillians in 1942,¹ the present report deals with the subacute and acute forms only. Chronic forms differ in many respects from subacute and acute forms. The chronic forms have characteristic cutaneous and mucous membrane lesions with specific features which are lacking in most of the more acute cases. Chronic cases have little, if any, systemic signs, their prognosis is generally favorable and they are amenable to therapy as contrasted to the subacute and acute cases in which the systemic disease dominates the picture and which in the great majority of cases end fatally. Yet there can be little doubt that these different forms represent just different courses of the same disease. The following observations are suggestive for their identity.

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‡ "Erythematoses" is the correct form for this adjective, erythema (genitive erythematos) being a Greek word, and "des" being the Greek ending for forming adjectives from nouns. "Erythematosus" is half Greek and half Latin and "lupus erythematosus" is grammatical nonsense.

§ Some dermatologists, following the trend in nomenclature to replace an adjectival noun by the more or less characteristic adjective alone, suggested the name "Erythematoses." Better names were suggested in the past. Unna's term "Ulerythema centrifugum," for instance, indicated a centrifugally spreading erythema with subsequent scar formation, which is a good and short characterization of the cutaneous lesions in the chronic forms.

1 Chronic lupus erythematoses may suddenly assume a subacute or acute course with fatal outcome, particularly under the influence of provocative or precipitating factors. This is relatively uncommon in the chronic discoid form with inveterated plaques but rather common in the chronic disseminate form and in cases with chronic lesions which are not fully developed but present only sharply circumscribed disks of dusky erythema and edema (so-called "erythema perstans")

2 In subacute lupus erythematoses the more persistent lesions often become clinically indistinguishable from lesions of the chronic form. This is particularly true of the lesions of the mucous membranes of the mouth.

3 Most histologic features are identical in all forms. From skin specimens the microscopic diagnosis of lupus erythematoses can easily be made in typical cases, but often it is impossible to say whether the lesion is from a chronic or a subacute or acute case.

4 In all forms ultraviolet light has an intensely provocative effect. Often the disease becomes manifest following sun exposure, or the disease already present exacerbates or even takes a fatal turn when the patient exposes himself to the sun. A similar but less obvious provocation is exerted by intense cold, wind and by heat in all forms.

5 In subacute and acute lupus erythematoses a most constant and characteristic laboratory sign is leukopenia. In chronic cases the white count tends to be at the lower border of normal values and on provocation, particularly by treatment with heavy metals, easily becomes subnormal.

SYMPTOMATOLOGY OF SUBACUTE DISSEMINATED LUPUS ERYTHEMATODES

The onset is gradual and the symptoms such as tiredness, weakness, loss of appetite, joint pain and muscle pain are rather vague in the beginning. The seriousness of the condition is usually realized only after several weeks when the temperature is found to be above normal, or a substantial loss in weight becomes evident or when cutaneous manifestations suddenly appear.

The most characteristic cutaneous lesion is the butterfly-shaped erythema of the face, consisting of pale to vivid red and more or less edematous well-circumscribed patches on both cheeks connected with each other across the nose. Bluish or purplish red patches around the nails and on the palmar surface of the fingers with a few fine telangiectases within the patches are another frequent and characteristic sign. Vivid red or bluish red edematous lesions can appear anywhere though with a definite predilection for uncovered parts of the body, particularly the face, neck, hands and forearms. The individual lesions may grow and be more inflamed in the periphery than in the center. Adherent scales are sometimes present but the characteristic



Fig 27—Generalized eruption in subacute lupus erythematoses with grouped inflammatory papules



Fig 28—Lesions of buccal mucous membrane and lips in subacute lupus erythematoses

follicular horny plugs of chronic lesions can hardly ever be seen. The extent and density of the lesions are subject to wide variations. The degree of inflammation also is greatly variable. For instance, the edema of the butterfly erythema is at times hardly recognizable, and at other times so intense that the whole face appears swollen and disfigured as in erysipelas. The inflammatory process may reach the stages of vesicle and bulla formation, particularly on the edges of erythematous-edematous patches. After rupture of the blisters, erosions



Fig. 29—Subacute lupus erythematosus with some features of the chronic discoid form.

and crusts form. The vascular damage may lead to development of hemorrhagic lesions, petechiae as well as large suffusions.

The duration of single elements shows great variety. Even in the same patient and at the same time some patches fade rapidly and do not leave any trace, others persist for weeks or months and heal with pigmentation which again will stay for a long time. More persistent lesions display scaling, dilated follicular pores and telangiectases, representing transitions to the chronic discoid form. However, subacute lesions do not heal with atrophy.

The *mucous membranes* are often involved "Silvering" of the vermilion border of the lips and bluish-white demarcated patches surrounded by vivid erythematous halos on the buccal mucous membranes across the closure line of the teeth may be identical in their clinical appearance with the lesions seen in the chronic form. However, in subacute cases the mouth lesions have more tendency to formation of painful erosions and edematous swelling. Involvement of the tongue, nasal mucous membranes, larynx and external female genitalia has been reported.



Fig 30—Circular infiltrated lesion with raised crusted edges in subacute lupus erythematoses

One of the most constant signs is *fever*. The subacute course is characterized by fever between 100° and 102° F. with little diurnal variation. Bed rest lowers the average temperature but does not bring it to normal.

Joint pain, usually without swelling and with no roentgenologic evidence of inflammation is a frequent occurrence. Sometimes, however, periarticular edema and/or induration are associated with joint pain and may result in slight limitation of motion, particularly of the small joints. They involve single joints or several joints at once, and migration from one group of joints to another is often encountered. Joint pain is often associated with muscular pain. Both can be so

intense that they disturb the patients in their sleep and make lying in certain positions highly uncomfortable. Tenderness of muscles can be the predominant symptom.

Urinary findings indicate inflammatory processes in the kidneys. Albumin is commonly 1 plus or 2 plus, and red cells are found in varying amounts in the sediment. Usually their number is not great, but if a persistent search is made red cells are always found. Great variation in the number of red cells is rather characteristic. All urinary changes are reversible for a long time, and regardless how long they last and how severe they are, urinary retention with azotemic signs does not develop except occasionally in the end stage of the disease. Hypertension is rarely present. When the renal lesion is suitably severe and prolonged, a nephrotic syndrome may be manifest and may even be the presenting picture.

Involvement of the serous membranes is characteristic. Pleural or pericardial effusion may be among the first manifestations or may appear later in the course. The fluid is a serofibrinous exudate with low leukocyte content. Diffuse abdominal pain is attributable to peritoneal involvement which provokes nausea and vomiting. Surgical exploration in such cases has had catastrophic consequences. A polyserositis of some degree is usually found at autopsy although the clinical picture may indicate fewer signs to be present.

In a high percentage of the cases a gross *endocarditis* is found at autopsy. Clinical symptoms may be entirely wanting or may have led to a false diagnosis of rheumatic heart disease. A soft systolic murmur is in itself not diagnostic of endocarditis, it can be the result of fever and anemia. There are no characteristic murmurs. Likewise, other cardiac, x-ray or cardiographic findings are not pathognomonic since there is no direct impairment of valve function. Heart failure is rare. Of diagnostic importance is the occurrence of white-centered petechiae, the presence of sterile blood cultures and absence of definite evidence of valvular lesions.

Lung involvement, clinically a patchy to confluent pneumonia (sometimes hemorrhagic), is usually complicated by secondary invading organisms. Otherwise, this pneumonia, like all the other manifestations, has its characteristic pathohistological features.

Enlargement of the lymph nodes, with some tenderness, is quite common, mainly in the neck, but this is not an outstanding sign. The enlarged nodes are tender but do not suppurate. *Enlargement of the spleen* has often been reported.

Enlargement of the liver may or may not be present. Liver functions may be impaired to different degrees. The patient may become jaundiced at any time and recover from it after greatly varying time periods. Like the disease of the kidney, the disease of the liver may be reversible for a long time.

Complications due to *central nervous system involvement* are not well understood but they often are quite striking, particularly in acute phases. In one of our cases death was preceded by a long period of marked mental stupor. More often there is great irritability, disorientation, random twitchings and tremor, simulating that of a Parkinsonian syndrome. Epileptiform seizures have been reported. Sudden blindness is due to either central nervous system involvement or to local retinal changes. More often retinal alterations can be observed ophthalmoscopically when there are no visual disturbances. Exudates,



Fig. 31—Acute lupus erythematoses with edema of the face and faint butterfly erythema

hemorrhages and edema occur in the absence of hypertension. Most patients in the subacute and even more in the acute phases are restless, apprehensive and conscious of the severity of the condition even though symptoms are few. We have heard from many patients that they knew they would die and it was always hard, if not impossible, to reassure them.

Among the laboratory signs, in addition to the urinary changes, *leukopenia* is by far the most constant and most pathognomonic single sign, particularly with regard to the differentiation of the disease from

rheumatic fever If the fever is not high, the count is practically always below 5000 In case of severe febrile complications due to secondary infections an expected degree of leukocytosis may develop, but the values drop conspicuously to subnormal levels as soon as such complications are overcome Counts as low as 1500 are not rare but such extreme low values are mostly transitory, bed rest and rational management are followed by a rise to from 3000 to 4500 In contrast to primary agranulocytosis, there is no progressive decrease in the number of polymorphonuclears as the disease progresses towards the end Persistent leukopenia in periods of high fever, however, indicates a poor prognosis

Anemia of the secondary type is common and can be severe. The sedimentation rate is markedly increased.

As constant as leukopenia is the *disturbance in composition of plasma proteins* There is a decrease in albumin and increase in globulin with an inverted A/G ratio The electrophoretic analysis of plasma proteins reveals a marked decrease in albumin and a pronounced increase in the gamma globulin fraction In our material the earliest change is the decrease in the albumin fraction In the more advanced cases this is accompanied by a relative increase in the gamma globulin fraction, while in the acute cases there is also an elevation of the alpha globulin.

In a high percentage of cases one or the other of the *serologic reactions* for syphilis (Wassermann, Kahn, Kline, Hinton) is positive It is rather characteristic for these biologically false positive reactions that they differ in strength in the different tests, change their titers rather irregularly independent of the severity of the course and seldom reach high titers The relation of these non specific positive reactions to the extraordinarily high gamma globulin values is not yet well understood

Blood cultures are constantly sterile except in cases of frank secondary infection occurring in the terminal phases In these phases both *Streptococcus hemolyticus* and *Streptococcus viridans* have been reported Lately, well-deserved attention is being paid to the rather constant finding of *Streptococcus viridans* in the urine

SYMPTOMATOLOGY OF ACUTE DISSEMINATED LUPUS ERYTHEMATODES

The differentiation of the acute and subacute types is based merely on the severity of the constitutional symptoms and the rapidity of the course Transitions between the two are common The subacute form may turn into an acute phase at any time with rapid fatal termination. On the other hand, in the genuine acute form prodromal signs and symptoms such as malaise, tiredness and joint pain can be traced back in the history, preceding the "acute onset" of the disease for many months Yet, prognostically there is one essential difference The typical

course of the subacute form is characterized by frank intermissions between the exacerbations. During these intermissions the patient feels perfectly well and all the objective signs may be absent. The disease may be present for several years before it enters a fatal phase. The acute attack, if interrupted at all, is capable of only incomplete and short lasting remissions.

In the acute form high fever sets in rather suddenly, and the patient appears seriously ill from the beginning. The fever with daily maxima at 105°F , sometimes at 106°F , even if not quite continuous, is not of the septicemic type. Differences between morning and evening temperatures usually do not exceed $1\frac{1}{2}^{\circ}\text{F}$. The protean character of the symptomatology and the variable order in which different organs become involved is even more pronounced in the acute than in the subacute form. *Cutaneous and mucous membrane lesions* can be entirely absent or recognizable only as pale macules in intense light, or, with all transitions between, there might be a dense, vivid red, exanthematic eruption simulating scarlet fever or measles. However, the characteristic butterfly erythema and bluish or purplish red macules on the hands and fingers are rarely missed. Their intensity changes from day to day. *Involvement of joints, muscles, kidneys, heart and serous membranes* is usually more severe than in the subacute form, but not necessarily so. The *apprehensive attitude* is more pronounced. Many patients are so agitated that they must be watched day and night and heavy sedation becomes unavoidable.

In the great majority of cases the course is stormy. The patient rapidly goes downhill and loses strength. Breathing becomes shallow, the pulse weakens and after a short comatose period death ensues. The duration is from a few days to a few weeks. As mentioned above, the course is rarely interrupted by short and incomplete remissions. It is a great rarity to see such a remission enter into the subacute phase for a long period of time.

LIBMAN-SACHS SYNDROME

This syndrome refers to a clinical entity which is indistinguishable from disseminated lupus erythematoses. There is a verrucous endocarditis with no Aschoff bodies present in the myocardium, negative blood cultures, petechiae of the skin and evidence of renal disease. Two out of four patients about whom Libman and Sachs reported in 1924 had eruptions similar to those of lupus erythematoses. Still, for a while it was not quite sure whether the two conditions were identical because in several cases, described since the original publication, skin manifestations were absent or fleeting. In 1938 Libman² agreed that the diagnosis of lupus erythematoses could apply to his cases, and for the great majority of observers there is no doubt that what

Libman and Sachs described were cases of lupus erythematoses, some of them without cutaneous manifestations

DIFFERENTIAL DIAGNOSIS

The clinical symptomatology of *rheumatic fever* resembles greatly that of acute lupus erythematoses. Differentiation on a purely clinical basis is often impossible, particularly if cutaneous and mucous membrane lesions are not present and cannot be elicited from the history. Among laboratory findings leukopenia is the most important differentiating sign. The finding of red cells in the urine also greatly favors the diagnosis of lupus erythematoses.

Dermatomyositis is a disease with many features similar to those of all forms of lupus erythematoses. Lupus erythematoses often displays signs of pronounced and extensive myositis clinically as well as pathologically. In the acute form muscular pain is due to acute inflammation of the muscles, and in the subacute form muscle weakness is the clinical expression of a more chronic myositis. The differences of cutaneous signs were recently discussed by O'Leary¹⁵ and by Keil.⁸ The lesions of dermatomyositis are more rose-pink in color (in our experience it is a different shade than the usual color of arterial hyperemia), and show more closely set telangiectases and pronounced edema. Later the edema is transformed into a lardaceous infiltrate which resembles trichinosis. Although the inflamed skin appears thin due to stretching, clinical signs of atrophy are not as clear-cut as in the end phase of chronic lesions of lupus erythematoses. On the other hand, tiny areas of atrophy resembling white spot disease are more common in dermatomyositis on the covered portions of the body than in lupus erythematoses. The posterior aspect of the neck is far more commonly involved in dermatomyositis, displaying diffuse pigmented patches, whereas in lupus erythematoses the involvement of the exposed V-shaped part of the frontal aspect of the neck is a highly characteristic feature. A mosaic of pruritic shiny papules with deepening of the natural folds between them ("pseudo lichenification") is often encountered in dermatomyositis, especially over the small joints of the fingers, whereas "lichenoid lupus erythematoses" lesions are rare. Single lesions of dermatomyositis are less sharply demarcated than those of lupus erythematoses. Hyperpigmentation all over the body simulating Addison's disease is one more differentiating feature of dermatomyositis. Such differentiation however, will hardly be necessary in the presence of the butterfly erythema or of the bluish red spots on the palms, palmar surfaces of the fingers and around the nails, these lesions are rather characteristic for lupus erythematoses.

Subacute bacterial endocarditis is often hard to differentiate clinically. Positive blood culture is the decisive differentiating factor.

PATHOLOGY

In this description only the most essential changes which are specific for subacute and acute lupus erythematoses, in the skin as well as in the internal organs, are listed. Reference is made to the detailed studies by Montgomery,⁶ Klemperer^{4,5} and Gross.⁷

The cardinal pathohistologic finding in all fully developed lesions is a progressive fibrinoid degeneration of the connective tissue with participation of collagenous fibers, ground substance and elastic fibers. The degeneration may end in complete necrosis with basophilic fragments of nuclei, fragments of cytoplasm and of connective tissue fibers, all set in the granular eosinophilic ground substance. In response to these changes there is an inflammatory reaction with marked dilatation of the blood vessels and dense perivascular and periglandular cellular infiltrates, consisting mainly of lymphocytes. In the skin, infiltrates surrounding cutaneous appendages are typical findings. At junctions of the connective tissue with epithelium and endothelium pronounced edema is present. In cutaneous lesions this edema culminates in a liquefaction necrosis of the basal layer and in the formation of "lakes" at the epidermal-dermal junction. Other epithelial changes develop in more chronic lesions as sequels to the connective tissue disease.

Proliferative and obliterative changes in the blood vessel walls are not characteristic signs of the disease,⁶ but in some cases the glomeruli of the kidneys display a peculiar hyaline thickening of the capillaries which appear rigid and resemble wire loops. In these "wire loop lesions,"⁶ the endothelial cells proliferate.

The warty lesions of the endocardium in lupus erythematoses can be differentiated by the characteristic histopathologic features from those caused by rheumatic fever and by subacute bacterial endocarditis. Grossly, the warts in lupus erythematoses are always found in the wedge beneath the valves, whereas in other forms they are on the valves.⁷

Some of the histologic findings indicate that lupus erythematoses is primarily a disease of the reticulo-endothelial system.⁶

ETIOLOGY

The cause of lupus erythematoses is unknown. Discussion of its etiology, therefore, has been purely speculative.

The uniformity and distinctiveness of the clinical course and histologic picture strongly points to a single but as yet undiscovered etiologic agent. Most authors are inclined to believe that this agent could be a specific micro-organism. A filterable virus has often been assumed but no evidence has been presented for this assumption. The disease has not been transferred to laboratory animals by injections of the patient's blood or diseased tissue.

It has been held by some observers that streptococci are involved in the pathogenesis. Some believe that streptococci reside in circumscribed foci and from there create a specific kind of toxemia, systemic lupus erythematosus is the clinical manifestation of this toxemia. Others assume that a primary disease of the reticulo-endothelial system gives rise to toxic disturbances that decrease the resistance of the body to other infections, mainly to streptococci.⁶ Attempts to remove foci or alleged foci in subacute and acute cases have often ended with catastrophic results. The systemically ill lupus erythematosus patient cannot stand such procedures, and, therefore, it is impossible to test the theory of focal infections in this way. It was mentioned that the blood in the great majority of cases is sterile, and streptococci are found only in rare instances in terminal phases of the disease.

There is a theory of multiple etiology which postulates that lupus erythematosus is a symptom complex, a specific type of reaction which is elicited by different causes in a person whose health is enfeebled by tuberculosis, by rheumatic fever or by toxins arising from bacterial foci. Also it has been claimed that the manifestations of lupus erythematosus are allergic reactions to different etiologic agents. Stokes¹⁰ describes the lupus erythematosus patient as an "allergic person furiously responsive to his infection with a broken or inhibited leukocytic defense." Such a description is justified when one remembers that any kind of vaccine therapy may elicit explosive and fatal responses. The only real evidence for lupus erythematosus having an allergic mechanism, however, are the reports of Barber¹¹ and J. G. Hopkins¹² on positive cutireactions to streptococci and staphylococci in a few cases of systemic lupus erythematosus.

In recent years the trend has been away from the theory that lupus erythematosus is in some way connected with tuberculosis. The tubercle bacillus has never been demonstrated in the lesions and findings of tubercle bacilli in the circulating blood could not be confirmed. Attempts to prove that tuberculosis occurs more often in lupus erythematosus patients than in the average population have failed and no correlation of the disease with tuberculin sensitivity has been found. The existence of an attenuated or filterable form of the tubercle bacillus was assumed when animal inoculations with tissue material were reported to be positive after several passages in guinea pigs. However these findings remained unconfirmed. Nothing has been left which would support the tuberculous etiology of lupus erythematosus.

Precipitating Factors—More is known about precipitating factors than about the original cause. As mentioned earlier in this review, the sensitivity to the *sunburn rays* of the ultraviolet spectrum is one of the most constant and most spectacular features of the disease. However, lupus erythematosus obviously is not a primary light sensitization disease as is, for instance, xeroderma pigmentosum. Though it is

true that the onset very often is preceded by exposure to sunlight, there are cases in which the history of ultraviolet provocation is completely lacking. Later the disease invariably progresses regardless whether the patient is protected against ultraviolet light or not. It seems that the unknown causative agent creates the light sensitivity which can be regarded as a sign but not as an etiologic agent.

Almost as harmful as ultraviolet light is *cold*. It was stated that many lupus erythematoses patients have a tendency to have cold and cyanotic hands, feet and cheeks. The authors saw onset of the disease during a severe siege of cold weather in two patients whose occupation forced them to be outdoors. Some patients claim that cold weather is particularly harmful when there is a strong wind. Peculiarly, exposure to excessive heat also was observed to have a provocative effect.

The *female sex* is predisposed to the subacute and acute forms of the disease. In different statistics the prevalence of female patients is given as from 3:1 to 7:1. This proportion has pointed to a possible role of estrogenic hormone as a provocative factor. Rose and Pillsbury¹³ found premenstrual accentuation of chronic discoid and disseminated lesions and tried to influence the course by administration of male sex hormone with questionable results. The senior author of this review saw prompt and complete cure of chronic discoid lesions in a young woman after temporary x-ray sterilization, and immediate reappearance of the eruption after the return of the menstrual period.

The *age* factor also seems to be important. The subacute and acute forms are predominantly diseases of young women between 17 and 30. The disease is rare in the prepubertal age and after the menopause. In males, too, adolescents and young adults are in the majority.

THErapy

Absolute *bed rest* is indicated in the acute and subacute forms. Physical effort to any extent is poorly tolerated and may cause flare-up of any sign or symptom, particularly of fever, joint pain and urinary findings. Feeling of weakness is always present and, therefore, one usually does not need much persuasion to keep the patient in bed. High caloric diet rich in vitamins and persuasion of the patient that it is necessary to combat his anorexia with all his will power are essential parts of the general care.

Up to recent times there have been only two drugs which can be safely stated to influence beneficially the course of subacute lupus erythematoses, namely, quinine and bismuth salts. In cases with no tendency to remission, in which low grade fever, leukopenia and urinary findings persist unchanged over periods of many months, the administration of either of these two drugs in the appropriate dosage may bring about immediate improvement and this improvement may end in complete remission.

Quinine is mild in its effect, and yet its administration must be started with great caution. We start with $\frac{1}{2}$ gram of quinine sulfate orally three times a day, and if this is well tolerated, we gradually increase the dose up to 2 grains three times a day. Higher doses do not improve the effect and are likely to cause complications such as tinnitus and dizziness. Small doses usually can be continued over periods of many months without any harmful effect. Quinine seems to bring relief and to prolong life even in the acute course. In spite of its obvious therapeutic action, however, quinine does not prevent exacerbations forever and it may happen that the subacute course will become acute during quinine medication.

Bismuth has to be administered with even greater caution because it may effect activation. Therefore, it is contraindicated in the acute and in the active phases of the subacute form. It seems, however, that if it is given during remissions, it prolongs these periods. The mildest form of bismuth therapy is the intramuscular administration of its soluble salts such as sodium bismuth tartrate which is rapidly excreted and does not form deposits in the muscle from which the rate of absorption cannot be controlled. Sodium bismuth tartrate 0.03 gm ($\frac{1}{2}$ of the 2 cc ampoule) is given twice or three times weekly over a period of six to eight weeks. Treatment must be discontinued if any of the signs or symptoms exacerbate. White count and urinary findings have to be watched closely. If insoluble bismuth salts, such as bismuth subsalicylate, are used, injections should be given not more frequently than once a week and not in higher single doses than 0.1 gm (1 cc. of the usual brands).

Gold salts, the most effective therapeutic agents in the management of the chronic forms, are absolutely contraindicated in the subacute and acute forms because of the danger of their activating the morbid process.

The unfavorable, often fatal consequences of vaccine therapy and of surgical procedures such as extraction of teeth, tonsillectomy and abdominal exploration have already been mentioned.

Blood transfusions often become necessary in order to combat anemia, but they do not essentially influence the course of the disease.

Penicillin in standard doses (24 million units in eight days) has proven to be ineffective in disseminated lupus erythematosus. Very recently, it was found¹⁴ that exceedingly large doses, such as 8 million units daily over three day periods influence the course of the disease beneficially. It is too early, however, to make definite statements as to the efficacy of this therapy. Sulfonamides are ineffective and possibly harmful.

Little can be done for symptomatic relief. Joint and muscle pain are better influenced by quinine than by salicylates. Local application of moderate heat to the painful areas is useful. Acute inflammation of

the mucous membranes of the mouth requires frequent washing and gargling with alkaline mouth wash and often a soft diet must be ordered to avoid irritation by solid food particles. Skin eruptions do not necessitate local treatment. In case of distressing burning sensation and marked edema dermatologic wet dressings with 2 per cent boric acid solution can be used.

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THE PSYCHOSOMATIC APPROACH IN GENERAL PRACTICE

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INTRODUCTION

THE recent tremendous upswing of interest in the psychosomatic approach to an ever-widening range of medical problems is encouraging. It is not a new concept by any means.¹ It is one of history's paradoxes that until relatively recent times the physiologic effects of human emotions were an important segment of medical knowledge. The vapors, emotional affections of the bowel, and systemic illness due to mourning or "heartbreak" were respectable ailments treated with serious purpose even though with techniques as outmoded today as are cupping, asafetida bags and laboring chairs. What happened to this knowledge until so recently? When and how did illness due to emotional factors become a thing so disgraceful that a patient should be insulted to be suspected of such a thing and graduates of the finest medical schools should have only impatience, disgust and a stern lecture for the miserable soul so afflicted?

The story of several hundred years stagnation in scientific thinking, as a result of the "unimpeachable authority" of Galen's brilliant teachings, is well known. It was a similar though less acknowledged historical event which seems to have been responsible for the stunting of knowledge in what we now call psychosomatic medicine.² In 1858 Virchow and his microscope completely revolutionized medical concepts, placing disease in cellular alterations. His was one of the greatest contributions in the history of medicine. From the impetus of his work came the devotion to the employment of the exact sciences to the study of disease. So revered were this man and his teachings that, eventually, anything which could not be measured in pH, would not obstruct passage of x-ray or could not be seen under a microscope—just did not exist. And any patient complaining of any symptom without measurable physical or chemical change was an anachronism—personally insulting the "gods" of scientific medicine by insisting that he was ill when physical and chemical laws said he was not. Even in the first World War, where the great numbers of invalids without measurable organic changes forced some recognition, the name "shell shock" insisted upon a *physical cause*.

While the medical profession, in general, continued rigidly confident

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of the all-inclusiveness of the purely organic approach to illness, there were a few men who came out of that war with the seeds that are now beginning to be harvested. Today we recognize that "psychic and somatic phenomena take place in the same system and are probably two aspects of the same process"² A psychologic approach to the one is as essential as is the physicochemical approach to the other. Properly, then, every practitioner, general or specialized, must have an appreciation of the emotional factors which may have caused, aggravated or prolonged the physiologic alterations and disturbing symptoms in any illness. Furthermore, he must have a real understanding of the simpler mechanisms by which the psyche and soma are inseparably linked. Finally he must use this knowledge in the treatment of the patient as a total organism.³

Unfortunately there are still too many physicians who honestly think they have fulfilled their obligation to the patient when they say, "There is nothing organically wrong with you. This is a nervous trouble. You're working too hard. Better slow up and take a vacation. Get your mind off yourself."

This is a failure in the physician's responsibility to the patient just as much as though upon discovering a temperature elevation in a patient complaining of night sweats, the physician were to say "Your sweats are due to fever. Go home and take some cold drinks and aspirin." What self-respecting physician would defend such a procedure?

"But that is a different situation," he protests. "I have no psychiatric training. And, if I did have, where would I get the time to do psychotherapy?" The answer to that is—one doesn't need to be a psychiatrist to help the majority of these patients, and as for the time element—an hour or two invested by the first doctor consulted for a psychosomatic disease may save himself and colleagues a hundred future fifteen minute periods of reassuring and successive examinations and treatments for new somatic developments.

INTERPRETATION OF FUNCTIONAL DISTURBANCES

If the physician considers the term *functional disturbance* in its literal sense, he eliminates the temptation to interpret the symptoms as "imaginary." He has now started his thinking in the right direction and finds the concept not at all difficult to explain to the patient. The term "functional" recognizes the fact that *there is a somatic abnormality*, a disturbance of the function of a given organ or tissue without necessarily any change in the cellular structure. Every layman is familiar with the phenomena of flushing or blanching of the skin in moments of anger or fear. Who has ever made his first platform performance or feared discovery of a misdemeanor without a dry mouth, sweating

palms, trembling fingers and a racing pulse? Severe anorexia, nausea, a tendency to diarrhea or constipation and frequent urination are all familiar symptoms at "exam" time

The only difference between these "normal" symptoms and psychosomatic disease is that in the latter the emotion is more chronic or "low grade," so that the patient may have failed to recognize the emotion's relationship to symptoms or, half recognizing a relationship, has not found means or courage to correct the situation responsible for his simmering anger (i.e., resentment) or smoldering fear (i.e., anxiety or guilt)

The physician who really appreciates this relationship and can explain it in simple terms to the patient will often find the cause of the difficulty with no further effort, or it may take two or three interviews to unearth the problem which has been hidden from the patient, or about which he feels too guilty or too embarrassed to speak at first. Many excellent, practical suggestions for conducting such interviews and evaluating the information gained are to be found in Whitehorn's brief "Guide to Interviewing and Clinical Personality Study"⁴

While the source of the trouble is being sought and dissolved, symptomatic relief for disturbing symptoms should be given, but *with the understanding of the patient* that these things are only a temporary crutch and not in any way intended as a cure

When the true emotional cause for the somatic disturbance is found, more often than not the physician may effect a gratifying result with a little common sense advice about interpersonal relationships for the woman with in law troubles, special agencies to help the father of a predelinquent or handicapped child, vocational guidance for the man who can't find his niche (A vacation won't help, if he goes right back as the same "square peg"), contraceptive advice for the woman who is fearful of pregnancy, or different living arrangements for the white collar girl who is in constant friction with her mother or some other member of the household

In some of these people, the circumstances may make it impossible to correct the situation at once. Still, the understanding physician can do much to help these individuals to face the issue and make a tolerable compromise, wherein they may be free of their symptoms most of the time and require moral support and symptomatic treatment only at periods of special emotional stress

In those cases in which the source of anxiety or resentment is not revealed in two or three leisurely discussions or in which the problem is not so simple (i.e., situational) as those mentioned above, the physician should refer the patient to some one with psychiatric training. If he, instead, simply gives up the search and reverts to methods of prolonged palliation, placebos, vitamin shots, iron and removal of foci of infection, he is failing in his duty to the patient just as truly as if

he failed to refer a patient to a surgeon who was competent to perform a needed operation which he, himself, was not trained to do.

The importance of evaluating the degree and nature of emotional factors to be taken into account in the management of any sick human being cannot be overemphasized. It is well to remember that physical illness always is accompanied by emotional components, however slight they may be.

ILLUSTRATIVE CASES

Case I. Functional Backache.—The first case to be presented illustrates the manner in which emotional factors may give rise to painful somatic responses threatening to produce disability

A 38 year old woman employee came, in tears, to the "Women's Clinic" at Lockheed Aircraft Corporation⁶ to request a medical "release" (This was at the peak of war production, when all workers were "frozen" in their jobs) She had developed intractable low backache which interfered with her rest at night and threatened to incapacitate her altogether Examination showed marked spasm and tenderness of all the back muscles without evidence of joint involvement. X-rays were normal.

Investigation revealed that this patient had been the first woman employed by the company as a spot welder In her two and one-half years of employment in the department she had never been absent a day and was rated as their most valuable worker Recently an efficiency minded "straw boss" had decided that it would simplify bookkeeping to assign the *same* operator and the *same* parts to the *same* machine permanently So, for six weeks this woman had stood constantly, welding awkward 10-foot wing sections, while the woman in front of her sat comfortably day after day welding pieces 6 inches square!

The "efficient" boss had forgotten the human equation When the situation was pointed out to the departmental supervisor, arrangements were made at once to rotate the less desirable work The top-flight welder stopped having tension spasm of her back muscles and continued as a valuable worker throughout the war

Comment—This is a fairly classical example of functional backache While it may be argued that constant standing played a role in the picture, experience with hundreds of such problems in industry proved that the muscle tension arising from smoldering resentment over "unfairness" in the work situation was far more significant.

In this instance, the patient actually preferred to stand at her work but resented being forced to do so

If she had been "released" because the work was "too heavy," her resentment toward the "inconsiderate company" would undoubtedly have persisted and with it, in all probability, the backache

Case II. Threatened Cardiac Invalidism without Organic Disease.—The second case illustrates the important point that circumstances do occur which make it necessary to prove the psychological origin of somatic symptoms *before* organic disease can be ruled out by the usual technics

A 27 year old Chicago housewife was admitted to the hospital on August 15, 1945 complaining of pains in the chest, dizziness, fainting spells and "vomiting blood." In 1941 she had had pneumonia. After two or three months of increased fatigability she felt very well except during occasional visits to Racine, Wisconsin, where she invariably experienced a tight feeling in her chest. She assumed that the dampness in Racine aggravated some residual from her pneumonia.

In May of 1945 her husband moved the family to Racine. She soon began to experience precordial tightness. Weakness and loss of weight became progressive. In July she fainted one morning upon getting out of bed. Twice, later in the day, she became dizzy and fell without losing consciousness. Because the dizziness and tendency to faint persisted, the patient was forced to remain in bed. Her local physician prescribed digitalis. A few days later she began to vomit. This symptom increased until on the night before admission there was an emesis of bright red blood.

Physical examination revealed marked weight loss (115 to 95 pounds in three months). The blood pressure recumbent was 138/80, upright 150/100. The pulse rate jumped from 90 to 120 on standing. The heart appeared to be of normal size and there were no murmurs. There was a fine tremor of the fingers. Extremities were cold. The blood count, sedimentation rate, urinalyses, fasting blood sugar, non-protein nitrogen of the blood and x rays of the gastrointestinal tract and chest were all normal. Total serum proteins were reduced to 4.6 gm. with slight inversion of albumin-globulin ratio. Vitamin A and C levels were below normal. The electrocardiogram was grossly abnormal and remained so following atropine given to eliminate functional (autonomic) interference.

It was difficult to arrive at a satisfactory diagnosis. Except for the rapid pulse and slight hypertension, the heart was normal on physical examination, yet the history of precordial distress, weakness, syncope and the definite electrocardiogram changes not be ignored.

In an attempt to leave no stone unturned, a more careful social-psychiatric history was taken. At 18 the patient married a boy she had known since childhood. This released her from a miserable family situation (Details omitted here). However the boy's parents strenuously disapproved of the marriage, rigidly resisting all efforts of the patient and her husband to win their blessing. It is noteworthy that the patient's first symptom (tightness of the chest) always occurred on visits to Racine—to the home of her husband's parents. The patient admitted that she had invariably dreaded these visits because his parents were always so "cool." They went out of their way to make cruel, cutting remarks which hurt her and her husband, frequently reducing one or both of them to tears. Between these visits the patient was perfectly well and happy with her husband and two children in Chicago.

When the husband was to be drafted into the Army, he moved his family to Racine, just three blocks from the parental home, with the idea that they could "look after her." The patient held up very well when he left and for two months thereafter while his sister lived with her.

When the sister in law left to take work out of town, the patient was alone in the house with two preschool children in a strange town. She had no diversion except for occasional visits to her husband's parents, where the atmosphere was always very stiff and cool. Her parents in law did not even manifest interest in the children and in spite of her husband's appeals never came to see her, their only explanation being they hadn't the time, which was not true.

During this period the tight feeling in her chest became increasingly persistent and frightening. A constricted feeling in her throat developed which made swallowing difficult. Anorexia became severe. She began to lose weight and strength. Fainting appeared. It was at this point that she was given digitalis.

A few days later her husband came home for a week-end. Although nauseated, she forced herself to eat a large meal which he had cooked for her. Soon afterward vomiting began and continued with violent retching for several hours. Eventually there were a few streaks of blood. (It was this which gave rise to the history of hematemesis!) Her husband, alarmed, brought her to the hospital that night by ambulance.

Armed with this proof of an adequate etiology for a purely functional disturbance of the heart, another electrocardiogram was made, this time following an injection of ergotamine tartrate instead of atropine. The resulting record was perfectly normal.

The facts were carefully presented to the patient. The comparison between her symptoms of tightness in the chest and constriction in the throat and the normal symptoms of "aching breast" and "lump in the throat," experienced by others at times of acute sorrow or hurt feelings, was readily recognized by the patient. The loss of appetite was likewise explained by additional analogies. The dizziness, syncope and progressive weakness were presumed to be the result of starvation plus some component of vasomotor disturbance, also due to emotional factors. The vomiting probably occurred as an effect of digitalis upon an already disturbed digestive function, and the bleeding was nothing more than might be expected from the trauma of violent retching for hours.

The patient, perfectly capable of understanding these explanations, accepted them completely and with conspicuous relief. However, in spite of her good insight into the functional nature of her illness, it was obvious that she lacked the fundamental intellectual and emotional resources to cope with the environment which had precipitated her illness and subsequent debilitation.

The obvious solution was for the patient to separate herself permanently from all contact with her husband's parents, yet it would be some time until she would be strong enough physically to take full care of her children and home. She could not afford to hire household help and, of course, any assistance from her husband's family would only have defeated its purpose. With the help of the Red Cross, arrangements were made for the husband's Army discharge. He had for some time suspected the source of his wife's trouble and was eager to correct the situation.

When last heard from three months after discharge, the patient was happily settled with her husband and children in another State. She was gaining weight, doing her own housework and except for a tendency to fatigue more than previously, was "as good as new."

Comment—This history illustrates the manner in which a common medical tragedy, the establishment of permanent cardiac invalidism without organic disease, was averted by enabling the patient to understand the *specific* emotional disturbances responsible for her illness and by aiding her to obtain an environment commensurate with her limited mental and emotional capacities. She was thus able to regain physical health and to resume her responsibilities as a housewife and mother of two small children.

Case III. Psychogenic Factors in Nonspecific Ulcerative Colitis.
—The third case illustrates the determinant role emotional factors may play in frank organic disease.

A 26 year old Army veteran, American born Japanese, was admitted to the hospital in a critical condition complaining of 15 grossly bloody, liquid stools daily, a weight loss of over 40 pounds in three months and extreme weakness.

In November 1944, while in France, he had noticed bright blood on his stools.

on three successive occasions. There was no pain, diarrhea or other symptom of illness at that time. This was at the time that his outfit was making the famous "lost battalion" rescue and living under the worst possible conditions, hygienically. In February 1945 he developed nausea and dizziness which necessitated three days rest. Ten days later he collapsed after a forced march. In the field hospital the diagnosis was combat fatigue and hypertension."

During his discharge examinations in June 1945, he complained of nausea and generally not feeling well. Upon returning to the Middle West he made arrangements to begin schooling toward the degree of Certified Public Accountant. Before he had actually enrolled, he suddenly began to have three or four bloody stools daily. He entered a Veterans Hospital and promptly began to have 40 stools a day. He lost strength and weight rapidly. No etiologic organism was found. On sulfonamide, paregoric and other symptomatic medication his stool count reduced to 15 per day but continued to be grossly bloody.

After several weeks, his condition being unimproved, he was transferred to our hospital where the diagnosis of nonspecific ulcerative colitis was confirmed. On diet, sedation and sulfathalidol his physical condition gradually improved. After five weeks he remained afebrile, was gaining weight slowly (5 pounds in five weeks) and stools numbered five daily with occult, but no gross blood.

Despite the gradual symptomatic improvement, the patient's morale and general appearance remained poor. He was moody and sullen, though not discourteous. He was several times discovered lying rigid in bed with his fists clenched and eyes tightly closed as though in pain or in panic. He had nightmares.

Finally in January 1946 he began to complain of "visions" that were disturbing him in the day time and expressed a desire to "talk to someone." This was arranged on January 7. For two hours there poured from him all his horror of war, blood and death, his resentment toward a persecuting lieutenant, toward the rigors and regimentation of Army life and toward the Veterans Hospital, and his guilt over certain incidents he considered dishonorable. The flood gates having been opened that night he called for the lotern and recited it all again. On the following day and evening the procedure was repeated with a noticeable lessening of tension.

On the day of the first interview the patient had no stools. Thereafter he had one formed stool a day with no occult blood. He gained 10 pounds in the next three weeks.

The patient's depression lifted remarkably following the "emotional catharsis." He began to eat better and his bizarre behavior ceased. However he still had periods of moodiness during which he expressed anxiety about the future. Further inquiry revealed that two days before the onset of his bloody diarrhea the following episode had occurred:

"My wife's employer said, 'I want to have a real father-son talk with you.' He said that we could live in their home as long as I wanted to go to school, and not worry about anything. Then he pointed out to me how I should have some better ambition. He showed me how there is no real future in accounting; you can go just so high and then you stay there. He said I should learn to do something where my income wouldn't level off like that at forty-five or fifty—And I can see that's right."

He was aware of having a general interest in mechanical and engineering lines but he had no knowledge of what such fields required beyond a mathematical background in which he was deficient and he did not have the prerequisites for a general college course. The patient was terribly disturbed after this conversation. He could no longer accept his former goal, for which he felt prepared and toward which arrangements had been completed. At the same time difficulties in the way of the new goal were overwhelming. Two days later bloody diarrhea began.

This source of anxiety about the future having been unearthed, the patient was encouraged to put down in black and white the actual pros and cons of various

careers he might choose and to list the questions to which he needed specific answers before making any definite decisions. That done, he was encouraged to concentrate upon the first step to be made in a broad general plan. That step was to take aptitude tests to ascertain where his best abilities lay before making any decision. That done, he could determine exactly what preliminary work he needed and where and how to get it.

From that time on the patient's progress was smoothly upward and continued so following discharge from the hospital on February 15.

Follow-up four and a half months later shows an almost completely normal mucosa in the rectum and sigmoid. The patient has regained his normal weight and is happily contemplating entering training as a mechanic with evident confidence in the future.

Comment—As the name implies, a specific cause and cure for non-specific ulcerative colitis have not yet been found. But since the report of Murray⁶ in 1930 concerning the striking coincidence of emotional disturbances preceding the onset or recurrence of bloody diarrhea, the importance of considering psychogenic factors in this disease has become evident^{7, 8}.

In this case the suppressed resentment and guilt, arising out of the patient's war experience, appear to have played some role in the illness. The anxiety concerning his future was precipitated acutely forty-eight hours before the onset of severe symptoms.

"Emotional catharsis" adequately relieved tension from the resentment and guilt, the anxiety was not difficult to relieve, by common sense advice, when its specific origin was found.

Case IV. Emotional Factors in Severe Bronchial Asthma.—The last case to be presented here illustrates the value of the psychosomatic concept in the treatment of severe bronchial asthma.

A 30 year old woman was admitted to the hospital with fever, chills, prostration, severe respiratory embarrassment, orthopnea and cyanosis. She had suffered from moderate asthma at intervals since childhood. Recently her asthma had been growing more severe in frequency and degree until she had experienced a severe attack of asthmatic bronchitis for two weeks prior to admission.

In the hospital the physical findings and laboratory examinations established the diagnosis of bronchopneumonia. Severe asthma so complicated the picture that she was critically ill for several weeks, requiring an oxygen tent constantly in addition to all the specific and supportive therapy.

Gradually the infection came under control, but the patient was still completely helpless with asthma, requiring frequent large doses of adrenalin and intravenous aminophylline.

It was a total of four months from admission until the patient was well enough to return to her home, where all suspected allergens had been systematically removed by her intelligent and very cooperative husband. The patient was delighted to be going home and confident that she would have no real difficulty.

Forty-eight hours later her distraught husband brought the patient to the emergency room in status asthmaticus. She was readmitted at once and placed in an oxygen tent. After two weeks she was able to be out of the tent in the daytime but required oxygen at night. It was noted casually that such daytime asthma as she had, tended to follow her husband's visits. The patient admitted being aware of this recurring coincidence. All possible allergens on her husband's person, such

as hair oil, shaving lotion and materials used in his work were checked, to no avail. After six weeks the patient was again thought well enough to return home.

Three days later she was readmitted with severe asthma and cyanosis. This attack was controlled fairly promptly so that in two or three days she was well enough to undertake the proposed psychosomatic approach to the history.

The role of the vegetative nervous system in bronchiolar spasm was explained to the patient. The possibility that the allergic condition might well be aggravated by emotional disturbances such as fear or anger was pointed out. The patient was willing to accept this possibility and eager to cooperate in any procedure which might possibly assist her to a reasonably normal life. She promptly volunteered that each of the recent asthmatic recurrences had begun a few hours following sexual relations with her husband. This was surprising, as they were an unusually devoted couple. She insisted that their marital relations were very pleasurable to her and that she invariably had complete satisfaction. Purely pleasurable emotions do not, presumably, cause illness.

Brief reconstruction of her personal history disclosed that when she and her husband married, ten years before, his mother had "laid down the law." She had already reared two families of children and she did not want any more of it. They were not to have any children. They could just take the precautions that she and her husband had used—withdrawal. They were young and ignorant of such matters. The mother was kind and "wise," respected and loved by them both. She did not in any other way interfere with their lives, so they felt obligated to comply on this point.

As the years went by, the patient began to hear and read things which alarmed her concerning the possible effects of this interrupted intercourse upon her husband. Each time they had relations she would lie awake for hours "stewing" over the harm this must be doing to him. As her fear and guilt mounted, her wheezing would begin.

It was a simple matter to correct the patient's misinformation. With her permission, the problem was discussed with her husband. Before her discharge, the patient was fitted with a diaphragm and given careful instructions for its use.

During the next year and a half of follow up the patient remained well, enjoying a normal active life with occasional mild asthma in bad weather.

Comment—This case illustrates the long recognized role of emotional factors in various allergic manifestations.^{9, 10}

In this instance, months of hospital care and medical (allergy) management gave disappointing results. Yet a "last resort" psychosomatic approach promptly resulted in satisfactory rehabilitation.

SUMMARY

It is the obligation of every physician to learn to evaluate the emotional factors in every patient and to treat those factors with psychological techniques rather than organic dodges. Lack of special psychiatric training or lack of "time" do not prohibit the constructive use of this concept. Case histories, representing problems in the fields of Industrial Medicine, Cardiology, Gastroenterology and Allergy, illustrate the value and feasibility of a psychosomatic approach in general practice.

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FUNCTIONAL UTERINE BLEEDING

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THE term functional is applied to abnormal uterine bleeding in the absence of organic disease of the reproductive organs. The bleeding is not in the normal pattern, and it can consist of an increased flow or a prolongation of the bleeding period, *menorrhagia*, or a complete irregularity of the menstrual pattern, *metrorrhagia*. The character of the bleeding periods, their frequency and duration, bear no relationship to the type or the degree of malfunction.

Abnormal uterine bleeding is the most frequent gynecologic complaint. In one of every three or four patients, no organic disease can be demonstrated in the pelvic organs and no systemic disease is present to account for this disturbance. It is most important to investigate every patient who complains of abnormal bleeding with great care in order that incipient organic disease, such as uterine cancer, is not overlooked.

Functional bleeding is encountered most frequently at two periods in life, the beginning and the end of the reproductive phase. It is not surprising that the developmental period should be disturbed in some young girls by irregular and at times profuse bleeding, since biologic functions rarely begin smoothly. The same is true of the termination of the childbearing period.

ENDOCRINAL-UTERINE RELATIONSHIPS

To understand the cause of functional bleeding, it is well to review the normal endocrinal uterine relationships. In the mature woman, cyclical changes are initiated in the ovaries by the anterior lobe of the hypophysis. One of its gonadotropic hormones, follicle stimulating in character (F.S.H.), exercises its action on the ovary, producing follicular growth and maturity of ova. At about the midinterval of the normal cycle, the second gonadotropic action of the pituitary gland, produced by the luteinizing hormone (L.H.), results in follicle rupture, the discharge of the ripe ovum and the conversion of the wall of the collapsed follicle into the corpus luteum.

The ovarian hormones control the changes that take place in the endometrium, and thereby the menstrual function. The growing follicle elaborates estrogenic hormone responsible for endometrial growth.

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The corpus luteum provides progesterin to convert this growing endometrium into a functional state, so that implantation can take place were the ovum to become fertilized. However, most often the ovum degenerates, unfertilized, and the progestational endometrium will undergo regression as part of the menstrual phase. Menstruation ensues when there is no implantation of a living fertilized ovum. If a pregnancy occurs, the chorionic tissue of the blastocyst will supply hormones which will maintain the activity of the corpus luteum.

The destructive phase of the endometrium and bleeding are brought about by a carefully correlated endocrinal mechanism that can be faulty in many places. These functional disturbances result in abnormal uterine bleeding. Sometimes it is possible to determine the cause, at other times our clinical acuity fails. Even though the cause is known, it is not always possible to correct the malfunction.

CLASSIFICATION

Functional Bleeding during Adolescence.—Puberty heralds the developmental period in the reproductive organs. The initial bleeding episode, and many irregular bleeding periods that follow, are not associated with ovulation. Bleeding occurs from an endometrium that has been stimulated by estrogens for a long time. The actual bleeding is probably associated with fluctuations in the level of blood estrogens. The exact mechanism is not understood, but this type of bleeding can be reproduced by the artificial administration of estrogens to a woman who has no ovaries. A drop in the amount administered or the cessation of its administration will result in a period of bleeding. In that it is not associated with ovulation, it has been designated as *anovulatory bleeding*.

Functional bleeding in adolescent girls and at the climacteric have the same underlying cause. With the onset of puberty the ovary is stimulated more and more by the pituitary gland. Follicles grow, but it may be several years before they reach a stage of development where ovulation occurs. During this developmental period the growing follicles secrete estrogens, which produce endometrial growth. Most of these follicles undergo regression by a process known as atresia. The ovum dies, the follicle wall slowly disappears. Some follicles continue to enlarge by an accumulation of fluid, reaching pathologic proportions, often remaining in the ovary for many months. Most of these follicle cysts no longer continue to produce estrogens (Fig. 32).

Bleeding occurs in the absence of ovulation from an endometrium in the proliferative phase. In some instances, this growth phase results in an unusually thick endometrium, in which folds may occur, and these may be converted into endometrial polyps by uterine activity. This hyperplasia is rather characteristic in that the endometrial glands

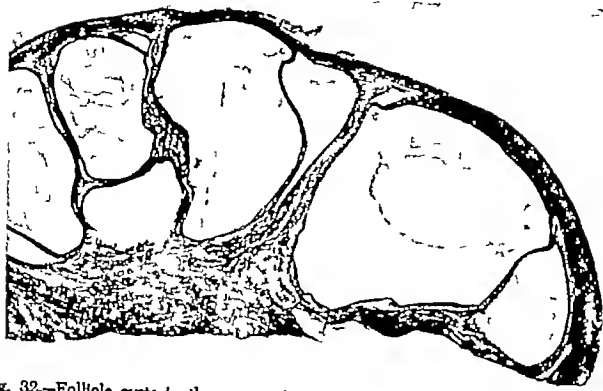


Fig. 32.—Follicle cysts in the ovary of a young patient with functional bleeding ($\times 10$)

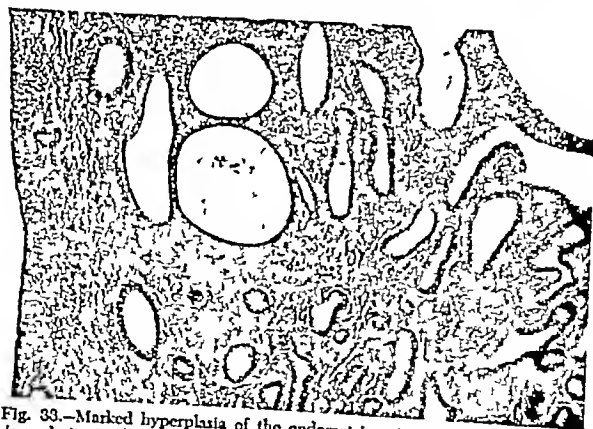


Fig. 33.—Marked hyperplasia of the endometrium in an adolescent girl. Note the irregularity in the size of the glands and the large cystic glands. No secretory changes are evident.

may become dilated or cystic, the epithelium, however, showing no secretory changes. The stroma is cellular, but the cells are not altered. A low power view of a cross section of such an endometrium will

show glands of varying sizes in an even background, providing the typical "Swiss cheese pattern" of Novak (Figs. 33, 34). The onset of bleeding probably results from a long-continued unopposed estrogenic stimulation, with varying levels of blood estrogen. The mechanism for this bleeding is not understood, but it probably involves the coiled arteries in the basal portion of the endometrium.

There is ample evidence to confirm the fact that the first menstrual periods in the adolescent are anovulatory in character. After one, two or three years, sufficient hypophyseal drive develops to result in a complete ovarian cycle. Ovarian follicles now reach full development, rupture and discharge their ripe ova. A normal menstrual pattern re-

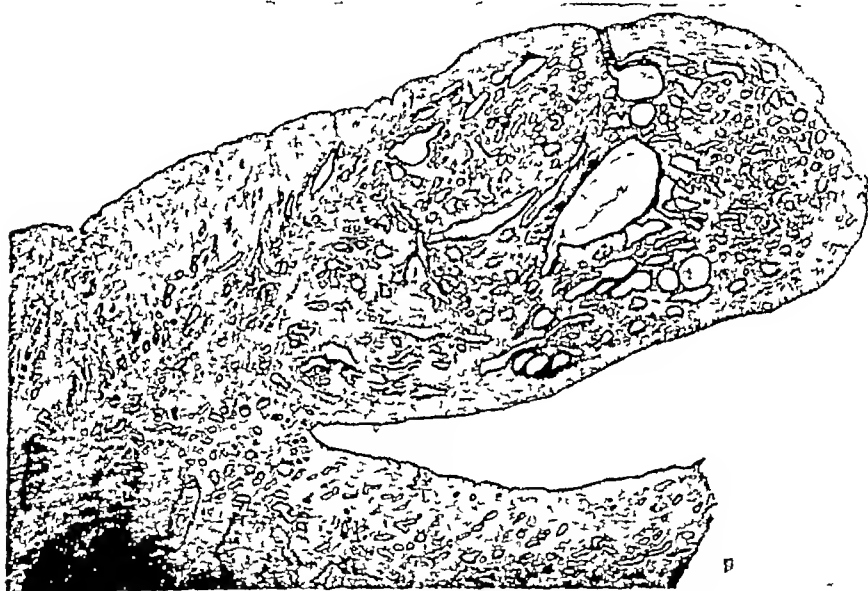


Fig. 34—Hyperplasia of the endometrium with marked polyp formation in a young woman of 28 with irregular bleeding for a year ($\times 12$)

sults, and the young adolescent has become a mature individual, capable of reproduction.

Functional Bleeding at the Menopause.—The termination of the reproductive period witnesses physiological changes similar to those that occur during adolescence, but in the reverse. The ovaries become more and more refractive to pituitary stimulation with the approach of the menopause. Thus, the woman will develop anovulatory bleeding periods, increasingly longer intervals between the periods, or a complete cessation of menstruation. There is no good evidence that the climacteric is associated with a transitory increase in ovarian activity. Conceptions occurring at this time represent a drop of the safeguards exercised by most women during their reproductive years, because they feel that pregnancy is no longer possible.

The irregular bleeding associated with the menopause represents long-continued estrogenic stimulation of the endometrium as in the adolescent period. Follicles grow to varying degrees, become atretic or produce follicle cysts. Occasionally, one reaches the point of development where ovulation takes place. The ovaries may contain many small or larger follicle cysts. The endometrium is of the hyperplastic type, sometimes polyps develop (Fig 35). This period will likewise end eventually when ovaries no longer are responsive to pituitary stimulation. Bleeding will cease completely, and the woman will be in the postmenopausal period.

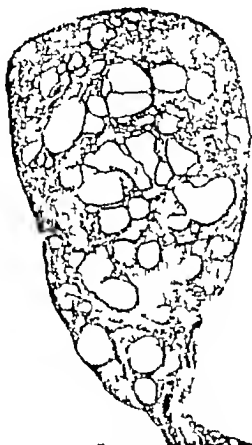


Fig. 35—A large endometrial polyp removed from a patient with functional bleeding in the menopausal period. Note the cystic character of the glands.

Functional bleeding in the menopause is far more serious than at any other period, for this is the "cancer age." Irregular bleeding is the *only* sign of cancer of the uterus, and so functional bleeding may easily mask an incipient cancer of the uterus. No one is ever justified in treating functional bleeding at this period of life until all measures to exclude cancer have been resorted to. A good rule to follow is never to consider irregular bleeding of the menopausal period functional until organic disease has been ruled out.

Functional Bleeding during the Childbearing Period—Functional bleeding can occur during the childbearing period. It may persist for months leading to a severe secondary anemia. It may cease

abruptly to be followed by a normal menstrual pattern. It may have its origin following a period of amenorrhea.

The *diagnosis* of functional bleeding during the reproductive years is more difficult, for the complications of childbearing are associated with bleeding. Abortion, ectopic gestation, hydatidiform mole and chorionepithelioma may have to be considered in establishing a diagnosis. Pregnancy tests, changes in the consistency and the size of the uterus and, occasionally, a diagnostic curettage will rule out these complications.

The cause of functional bleeding in young women is still not clear. As in other periods of life, it is probably endocrinal in origin. Normal cyclical activity ceases, usually temporarily, and the ovaries may develop numerous follicle cysts. Corpora lutea are conspicuous by their absence. With few exceptions, the bleeding occurs in the presence of a hyperplasia of the endometrium of varying degrees, and in the absence of progestational changes. Rarely, some portions of the endometrium may show secretory changes. The origin of the difficulty is not easy to ascertain. It is rarely in the ovaries, more often in the anterior lobe of the hypophysis, or in some other locality, and occasionally in the thyroid gland. The difficulty in determining the cause interferes seriously with the therapy of this condition.

TREATMENT

Functional Bleeding during Adolescence.—Functional bleeding during adolescence may need no specific therapy. The complication is definitely limited in duration, and will disappear as the young girl passes through adolescence into maturity. Active treatment is necessary if the bleeding periods are very prolonged and lead to a serious drain on the blood.

Efforts should be directed toward maintaining the youngster in good health. Outdoor exercise and plenty of sunshine should be stressed, for most mothers restrict the activity of their daughters at the first sign of irregular bleeding. Nutritional faults should be corrected, and a well balanced diet, rich in proteins and vitamins, advised. Postural exercises may help some girls who have developed faulty habits. These simple measures will suffice in a large number of cases, and are preferable to organotherapy.

The young girl who has bled sufficiently to embarrass her blood picture should receive more active treatment. A careful physical examination, including x-ray examination of the chest, should be made to rule out the presence of disease. The patient with a marked anemia should be brought into the hospital. Blood transfusion is the most expedient method of restoring the blood loss rapidly. Usually, a dilatation and a curettage is advisable. This procedure is the most rapid and efficacious method for stopping the bleeding. Furthermore, it pro-

vides endometrium for study and an opportunity for a good pelvic examination, which is often difficult in these young girls

A basal metabolism will reveal the state of the thyroid function. The thyroid gland exercises an important role in the endocrinal regulatory

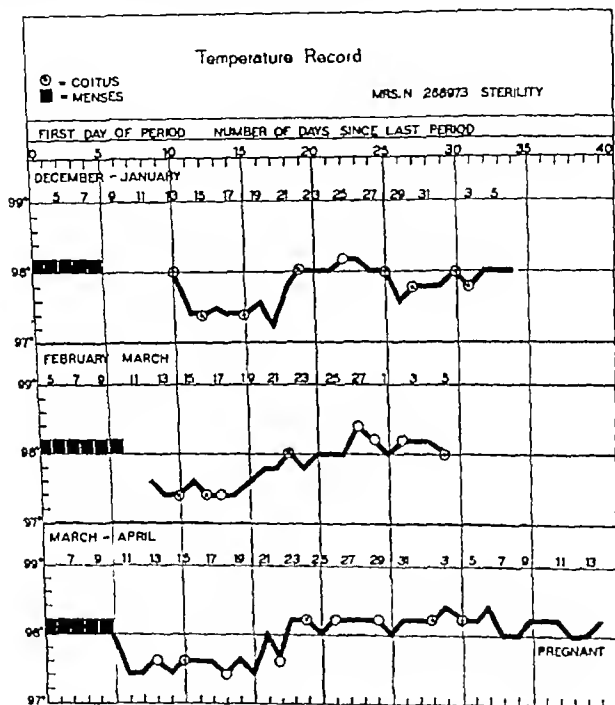


Fig. 36—Basal body temperature graph showing the normal pattern. Note the low temperature following menstruation, the rise during the ovulatory period and the maintenance at the elevated level for the latter half of the cycle. Twenty four to thirty six hours prior to menstruation the temperature starts downwards. If pregnancy intervenes it will remain at the elevated level.

mechanism of the reproductive organs. The thyroid exerts its action on the ovaries through the pituitary gland. Moderate degrees of hypothyroidism may result in disturbed ovarian activity. If the basal rate is low, thyroid extract should be administered. Usually 1 grain of

thyroid extract can be given for each minus 10 of the basal rate. Active youngsters should receive less thyroid substance than adults, and it is contraindicated in the thin, undernourished, nervous individual.

Functional Bleeding during the Childbearing Period.—Functional bleeding during the reproductive period calls for a careful survey of the patient's history, and a complete physical examination. A diagnostic curettage is indicated in order to rule out intrauterine pathology, and to provide endometrium for study. A basal metabolism should be routine.

Basal body temperatures can be used to study the ovarian cycle as well as to obtain an accurate record of the bleeding periods and to evaluate the result of medication. The temperature graph should form an important part of each patient's record.

Body temperature variations in healthy individuals have been known for many years. They are sensitive indicators of physical as well as mental activity, metabolic activity and other physiologic functions. Muscular work, food intake or mental excitement tend to raise the level of the temperature in the healthy individual. Typical curves have been set up demonstrating these fluctuations during a twenty-four hour period under varying conditions. They follow what is known as a diurnal pattern, for the temperatures during the night are lower than those recorded during the day, the nights being devoted to rest, and the days to activity.

In the healthy male, there is no variation in the daily pattern of the body temperature curve, other than that induced by the above factors. In the female, on the other hand, the normal function of the ovaries alters this basic curve. The body temperature remains at a low level during the first half of the month, but with ovulation and corpus luteum formation, it rises during a period of twenty-four to thirty-six hours, reaching a plateau where it will remain as long as the corpus luteum is active. Some twenty-four to thirty-six hours prior to the onset of bleeding the temperature will drop, reaching the baseline established during the first half of the cycle. In the event that pregnancy ensues there will be no drop in the temperature (Fig 36). In functional bleeding there will be no typical rise in the temperature, but irregular fluctuations may occur throughout the month. The return of a normal ovarian cycle will be heralded by a typical temperature curve.

The patient is instructed to take her temperature orally immediately on awakening each morning, and to note it on a specially prepared graph. A daily temperature reading each morning will provide a useful graph in three of every four women. Bleeding should be noted, as well as medication and other factors that could influence the body temperature.

Organotherapy

All of the hormones involved in the process of reproduction, alone or in combination, have been suggested for the therapy of functional bleeding. This fact is sufficient to emphasize that no one endocrinal substance is specific in its action, and that hormonal therapy is still in the experimental stage. If this therapy is used, potent preparations should be selected, and their application should conform to physiologic principles.

GONADOTROPINS—If the failure of normal cyclical changes is in the pituitary gland, the motor of the sex function, it is logical to think that gonadotropins should prove useful. There are three types of these preparations, derived from different sources, and exhibiting different actions. *Chorionic gonadotropin* is derived from pregnancy urine. In laboratory animals it will produce ovulation and corpus luteum formation, but its action is predominantly luteinizing. There is no proof that it will stimulate the human ovary, and there is evidence that it will produce follicle atresia. *Equine gonadotropin* stimulates follicular maturation, ovulation and corpus luteum formation in the intact and hypophysectomized animal. However, it will not stimulate follicular maturation and ovulation in the ovaries of women with functional bleeding. *Hypophyseal gonadotropins*, or extracts of the anterior lobe of the pituitary gland, will stimulate follicle growth in the human ovary, and possibly produce ovulation. The only potent preparations have been used experimentally and are not available for clinical use. They offer considerable promise, but at the present time there are no commercial gonadotropic preparations of value in the treatment of functional bleeding.

PROGESTERONE—If functional bleeding occurs in the absence of ovulation and corpus luteum formation, the substitution of progesterone should correct the endocrinal unbalance and result in a cessation of bleeding. Treatment is best instituted about two weeks after curettage. If this procedure is undesirable, it can begin at any time. At least 10 mg. of progesterone is administered intramuscularly each day for five or six days. Usually, bleeding will recur two or three days after the cessation of therapy, or, if it has continued, there will be an exacerbation of bleeding. This bleeding is associated with the breakdown of a progestational endometrium, and should last the average length of a menstrual period. Therapy should be repeated in about three weeks. It has been suggested that this procedure should be continued for about four or five months, following which a normal pattern may be established. *Pregneninolone* is a progesterone preparation that can be administered orally. About five times the parenteral dose should be given, for it is about one fifth as active as progesterone.

ESTROGENS—Estrogenic preparations are used for the treatment of functional bleeding during the childbearing period. Large daily doses,

5 to 10 mg. of stilbestrol, for a period of six or eight days, will often result in a cessation of bleeding. Since most patients already have estrogens, this procedure is not physiologic. Its effectiveness in the control of bleeding may be due to the fact that the threshold for bleeding is reached quickly and the increased amount of estrogens results in a precipitous drop and a breakdown of the endometrium occurs more rapidly. It may act directly on the endometrial vessels. There may be a recurrence of the abnormal bleeding, so that medication will have to be repeated. Hamblen and his associates have recommended that progesterone should follow the administration of estrogens, and that they should be repeated cyclically.

ANDROGENS—Androgens are useful in the control of functional bleeding. There has been some criticism as to their use, because they are unphysiologic, and large amounts will produce evidences of masculinization in the form of an increased growth of hair, enlargement of the clitoris and change in the voice. However, therapeutic amounts will not result in any undesirable effects and can be used safely. Some young women complain of a mild acneform eruption, which disappears when the hormone is stopped. If it is used parenterally, no more than 250 mg. of *testosterone propionate* should be given in any one month in daily doses of 25 mg. The oral use of *methyl testosterone* is equally effective, but larger amounts are necessary. About 30 to 50 mg. a day for ten days or longer is necessary to control the bleeding.

Following the administration of androgens, a period of amenorrhea of varying lengths will ensue. Abnormal bleeding may recur, and the androgens may have to be repeated. It is not known whether androgens act by inhibiting the anterior lobe of the pituitary gland, thereby suppressing estrogen secretion, by neutralizing the effect of the hormone on the endometrium, or by a direct effect on uterine blood supply through its action on the myometrium. In normal women, androgens will interfere with ovulation, at times inhibiting it, and at other times delaying its occurrence. Their efficacy in the treatment of dysmenorrhea is often the result of a suppression of ovulation and a subsequent anovulatory menstrual period.

Functional Bleeding in the Menopausal Period.—The treatment of irregular bleeding at the climacteric involves several important principles. In the first place, the possibility of cancer of the uterus must be ruled out by a careful examination, the visualization of the cervix and biopsy of any questionable lesion, and a diagnostic curettage in the absence of gross pathology. Secondly, if malignancy of the pelvic organs as a cause of bleeding has been ruled out, the onset of the amenorrhea of a natural menopause can be awaited, unless the bleeding is considerable and troublesome. In the third place, if the bleeding should be stopped, some procedure leading to an artificial

menopause should be adopted. Lastly, endocrine therapy must never be used for the control of functional bleeding at this time.

SURGICAL TREATMENT—Benign bleeding of the menopause can be treated by the removal of the uterus, if there are no contraindications to surgery. An abdominal or a vaginal hysterectomy is the treatment of choice. At times, it may be necessary to resort to surgery in young women in the late twenties, when other methods for the control of functional bleeding fail. In these women, ovarian function can be saved. The ovaries, if they are normal, may or may not be left in the woman in the menopausal period. Many clinicians feel that these structures have outlived their usefulness, that they remain as potential sites of neoplasms, particularly carcinoma, and that they are better out. This is a logical decision in the woman who is not sentimentally attached to these senile organs.

IRRADIATION—Irradiation used for the control of functional bleeding in the menopausal period is effective by destroying the remaining ovarian function. This may be accomplished by the intrauterine insertion of radium or by the use of deep x-ray therapy. Irradiation is as effective a method for the control of irregular bleeding in this group of patients with normal pelvic organs as is surgery, provided there is a proper selection of cases. There should be little or no hazard in this selected group of cases and the results are excellent in at least 98 of 100 patients. Contraindications are extremely important in the selection of therapy.

The **CONTRAINDICATIONS** to irradiation in this *selected* group of cases are:

- 1 *Uncertainty as to the extent of the pathologic involvement* Whenever it is impossible to determine the exact state of the pelvic organs, surgery is preferable to radiation.

- 2 *Inflammatory conditions of the reproductive tract*, particularly the adnexa, contraindicate irradiation.

- 3 *Previous pelvic surgery* After all pelvic operations, loops of bowel may become adherent to pelvic structures. In the normal patient peristaltic action results in the constant motility of loops of intestine, so that over-radiation of any one segment is unlikely. Too much irradiation of the bowel at one site may be followed by damage and stricture formation.

- 4 *Radiophobia* X-ray, radium and cancer are so closely associated in the minds of many patients that the use of radiation for the control of their bleeding may be followed by undesirable mental reactions. It may be impossible to convince the patient that she does not have cancer, and even though the bleeding is stopped she may develop a pronounced cancerphobia. Such patients are best treated by surgery.

Technic of Irradiation

X-ray Therapy.—Deep roentgen therapy is directed not at the uterus but at the ovaries. Ovarian function must be destroyed if a successful result is anticipated. In most instances the delivery of 400 roentgen units to each ovary will produce a permanent cessation of function. While smaller doses may produce the same effect in some individuals, there is no method for measuring the resistance of an individual ovary to x-ray therapy. Consequently, an amount of treatment which has been demonstrated to be effective in a large group of patients should be utilized.

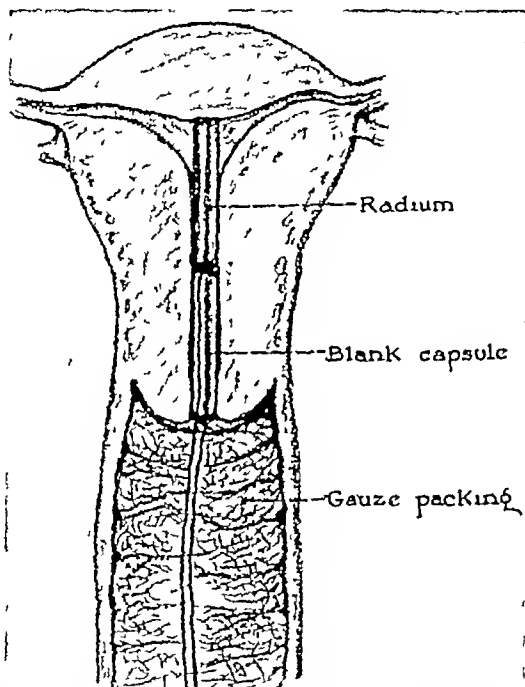


Fig. 37—The proper technic for the application of radium in the treatment of functional bleeding in the menopausal period

The skin dosage is of much less importance than the amount which reaches the ovary. The total amount of radiation to be delivered to each portal is determined by the anterior-posterior measurement of the pelvis at the symphysis and a calculation of the percentage of loss at the middle of the pelvis. The amount of irradiation to be delivered to the skin portals to produce castration may be calculated from tables set up on this basis.

Radium.—The action of radium is twofold. The most important effect in the treatment of benign bleeding is the inhibition of ovarian function. In addition, there is a local effect upon the endometrium, resulting in sclerosis of the mucosa as well as of the vessels in the

uterine wall Because the effect on the ovary is more important than the local destructive action and since too extensive local effect may result in a nonhealing chronic ulceration of the uterine wall, the penetrating gamma rays must be fully utilized. Extensive local destruction is produced by the soft beta radiation and these must be eliminated as completely as possible The enclosure of the radium in capsules with a filtration capacity equivalent to that of 2 mm of brass will remove all the beta radiation from the original rays. The passage of the radiation through the capsule, however, sets up secondary radiation, part of which consists of alpha and beta rays If the capsule is enclosed in a few millimeters of an organic substance such as rubber, the alpha and beta rays are almost completely filtered out and the resultant radiation consists almost entirely of penetrating gamma radiation which produces a minimum local tissue effect.

To produce the best effect the source of radiation should be concentrated near the tissues upon which the effect is desired (endometrium and ovary) Hence, the capsule should lie in close approximation to the uterine wall and should be within the body of the uterus Radiation of the cervical canal is undesirable because it is ineffective in accomplishing castration and the destruction of the tissue may be followed by scar formation and cervical stenosis The most effective and least dangerous method of applying radium for castration is illustrated in Figure 37, in which two capsules are inserted in tandem The upper one, in the uterine cavity, contains the radium and the lower one, in the cervical canal extending through the internal os, is empty

The total amount of irradiation necessary to produce castration consistently is about 1800 to 2000 milligram hours In some individuals, ovarian function can be inhibited by less but to insure consistent control of bleeding in a high percentage of cases, the dosage must approach this amount The duration of the application depends upon the amount of radium used. However, in most instances no more than 50 to 100 mg. of radium are necessary The capsules are not removed from the uterus until the full dose is given unless some indication for removal arises

The action of radium in controlling bleeding is not immediate since it depends upon loss of ovarian function as well as local changes in the uterus The effect may take place over a period of three to six weeks and there may be one, rarely two, bleeding periods following treatment.

THE RH FACTOR

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In a previous paper published in the January, 1944 number of these Clinics I briefly summarized the facts which were then known concerning the Rh factor, its relation to erythroblastosis fetalis and to intragroup blood incompatibilities. Later in 1944 the subject was discussed more exhaustively and the reader is referred to that paper¹ for a detailed account of the investigations which had been published up to that time. Since then several excellent reviews have appeared and the majority of all local and national journals have carried papers in which case reports have been prefaced by short summaries of the discovery of the Rh factor and of the work which has established its relationship to certain clinical problems.

As a result of these numerous publications, information concerning the Rh factor has become widely disseminated and it is useless to continue repeating the details of the early investigations. The present paper is an attempt to call attention to some of the more recent developments. For more detailed information the original papers must be consulted.

INTERRELATIONS OF THE Rh AND Hr SUBGROUPS

At the time of the initial recognition of the Rh factor it seemed that human blood could be differentiated into two varieties: Rh-positive which possessed the Rh factor and Rh-negative in which it was lacking. It was soon found, however, that Rh was not a uniform entity but was composed of several fractions which might exist individually or in various combinations. The three whose existence has been established are at present called Rh₀, Rh' and Rh'' and are found in the erythrocytes of about 85 per cent, 70 per cent and 30 per cent respectively of all white races that have been studied. Each is capable of antigenic activity and can elicit the production of specific antibodies when introduced into the circulation of susceptible individuals. The three antibodies are designated anti-Rh₀, anti-Rh' and anti-Rh'', the names corresponding to the Rh type responsible for their formation.

When one form of Rh is present alone, the blood is designated as of Rh₀, Rh' or Rh'' type. However, Rh' and Rh'' are rarely found except in association with Rh₀ and when either of these combinations

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exists, the bloods are designated Rh_0' and Rh_0'' , or for greater ease, Rh_1 and Rh_2 respectively. When all three are present the designation has been Rh_0''' , Rh_1Rh_2 , or most conveniently Rh_z . The combination of Rh' and Rh'' is called Rh''' or Rh_x .

The original antibodies which were produced experimentally and the human antibodies which were first recognized were of the anti- Rh_0 variety. This is the only kind which it has been possible to obtain from animals and is the one which has been most commonly observed in human subjects when immunization to an Rh antigen has occurred. Consequently, this is the only type of serum which is widely available for Rh testing. By its use not only are those individuals lacking all fractions of the Rh antigen considered Rh negative but those belonging to Rh' , Rh'' or Rh_x groups are Rh negative as well. Only bloods containing Rh_0 (types Rh_0 , Rh_1 , Rh_2 , Rh_z) fall into the Rh-positive group. Fortunately Rh' and Rh'' are rarely present by themselves, and since they seem to be less potent in their antigenic capacities the fact that their presence or absence cannot be demonstrated by the ordinary anti-Rh testing serum is not of great clinical importance.

It must be remembered, however, that individuals who are Rh-negative with the ordinary serum may belong to groups Rh' , Rh'' or Rh_x and that those who are Rh-positive with the standard serum may be lacking these same fractions. Because of this an Rh-positive person, as the term is generally used, may possess anti-Rh agglutinins. The variety of Rh antigen possessed by the person and the variety causing his immunization must be different.

Not long after the Rh factor was discovered an Rh positive patient was observed whose blood contained antibodies reacting with all Rh negative blood and with some Rh-positive blood. These antibodies were designated as anti-Hr because of their seeming relationship to anti-Rh. Other somewhat similar serums were subsequently found and two varieties of anti-Hr agglutinins which indicate the presence of corresponding Hr antigens have been definitely identified and a third, still undiscovered, is believed to exist. These serums give reactions which are complementary to the three anti-Rh serums. If cells fail to combine with the antibodies in any specific anti-Rh serum, they will invariably combine with those in the corresponding anti-Hr serum.

It seems apparent that the collective fractions of Rh and Hr are allelic, Hr being recognized as an antigen with a dominance equal to Rh. Before serums capable of establishing the presence of Hr were identified, all bloods failing to react with anti-Rh serums were considered Rh negative and the Rh negative character, written rh, was believed recessive to Rh ($Rh+$). Hr should now replace rh in all genetic considerations.

There are three recognized Rh antigens, Rh_0 , Rh' , Rh'' which, as stated previously, may exist alone or in combination. It had been

postulated that these are inherited by means of eight allelic genes four of which are single, rh , Rh_0 , Rh' , Rh'' , and three of which are double, Rh_1 , Rh_2 and Rh_x , and one of which contains all of the antigens, Rh_z . Each of the last four may act as two genes when transmitted to offspring, they usually remain combined but may be broken up into the two component parts (Rh' and Rh_0) (Rh'' and Rh_0) and so on.

Now that the identification of two Hr antisera and their corresponding antigens has been accomplished and it has been shown that each antigen is allelic to a specific Rh subtype, it seems reasonable to assume that inheritance may be by means of double alleles on each of three loci of a chromosome, the alleles being Rh_0 and Hr_0 , Rh' and Hr' , and Rh'' and Hr'' instead of by means of a group of Rh or Hr fractions in a single gene. Each chromosome must then carry one and only one member of each of the three pair. Eight possible combinations exist.

If only one chromosome were involved in the establishment of genetic pattern it would be possible to determine the genotype of any individual by the use of three anti-Rh serums. However, since there are two chromosomes each of which may have any one of eight Rh-Hr combinations, it is only by the additional use of three anti-Hr serums that a complete gene pattern could be obtained. If the three varieties of anti-Rh and the three varieties of anti-Hr serums were available it would be possible to differentiate twenty-seven of the thirty-six different types of blood postulated by the multiple allele theory, or all twenty-seven types postulated by the triple gene theory.

In order to make it easier to understand and to remember the genetic pattern, a suggestion has been made that capital letters C D E be used to indicate the presence of genes responsible for the three Rh fractions and corresponding lower case letters be used for the presence of the three Hr fractions.

C	D	E	c	d	e
Rh'	Rh ₀	Rh''	Hr'	Hh ₀	Hr''

An individual whose blood was homozygous Rh_1 would be designated $\frac{CDe}{CDe}$ and his genotype would be established by the fact that his cells would react with anti-Rh', anti-Rh₀ and anti-Hr'' serums and would fail to react with anti-Rh'', anti-Hr' and anti-Hr₀ serums.

An individual, on the other hand, whose cells were heterozygous Rh_1 would be designated $\frac{CDe}{cde}$ and his genotype would be established by the fact that his cells would react with all serums except anti-Rh''.

Another suggestion has been made for the substitution of numbers for the six serums listed above, arranging them in the order given, and following Rh by the numbers indicative of the sera which give posi-

tive reactions Thus homozygous Rh_1 blood becomes Rh 126 and heterozygous Rh_1 blood becomes Rh 12456

In the few laboratories where all three anti-Rh serums and anti-Hr' serum are available the genotype of the majority of individuals can be established However, since only one or two anti-Hr'' serums have been recognized and no anti-Hr₀ serum has been found, a complete genetic analysis of the Rh constituents of all bloods is as yet not possible.

AGGLUTINATING AND BLOCKING ANTIBODIES

The original antibodies which were demonstrated were all agglutinins in spite of the fact that they reacted as hemolysins within the body Subsequently the existence of another variety of Rh_0 antibody was discovered, which was capable of combining with any cell containing the Rh_0 antigen but was incapable of causing agglutination If cells were exposed to this antibody and later were added to serum containing anti-Rh agglutinins, they failed to become agglutinated—the action of the agglutinins was blocked by the action of the other antibodies These antibodies have been designated as blocking, partial, incomplete or thermostabile antibodies because of the characteristics they manifest Blocking antibodies of specificity Rh' and Rh'' and Hr' have also been recognized but they appear to be very rare

Blocking antibodies and agglutinating antibodies specific for the same Rh subgroup may be found together or either may be found alone, in exceptional cases the specificity of the blocking antibody may differ from the agglutinating antibody It seems possible on rare occasions that the introduction of Rh_1 ($Rh_0 Rh'$) cells may be responsible for the production of agglutinins against Rh' and blocking antibodies against Rh_0

The clinical importance and the relative significance of agglutinating antibodies in contrast to blocking antibodies has not been established Both are evidence of immunization and the statement has been made that agglutinating antibodies appear first and are later supplemented or replaced by blocking antibodies, the presence of the latter indicating a greater degree of immunization Blocking antibodies are demonstrable in the circulation for longer periods of time than are agglutinating antibodies and they may sometimes be found many years after they have once made an appearance The concentration of agglutinating antibodies usually diminishes more rapidly but they, too, occasionally persist for many years

RH FACTOR IN TRANSFUSION

The principal advances that have been made since 1943 in the study of the Rh factor have been in the fields just described, namely, in the further elaboration of the interrelations of the Rh and Hr subgroups and in the discovery of the thermostabile blocking antibodies.

The importance of determining the Rh as well as the AB blood group prior to transfusion had been established before 1944. It had been shown that introduction of Rh-positive blood into some Rh-negative individuals resulted in the formation of Rh antibodies. One injection of blood rarely causes immunization and in some individuals no immunization is ever produced regardless of the amount of Rh-positive blood, the number of injections or the time interval between injections. After immunization has once been established Rh-positive blood will be rapidly destroyed if injected into the blood stream of such an individual. The severity of the reaction will depend on the degree of immunization and the amount of blood injected. Death may occasionally follow.

Immunization of the female as a result of Rh-positive transfusions will ordinarily cause erythroblastosis fetalis in all Rh-positive offspring who are born after the immunization has occurred. A large share of the women who give birth to erythroblastotic babies in a first pregnancy have been immunized in this way. Consequently no female either prior to or during the reproductive period should be transfused without having the Rh status determined. Except in extreme emergency, only Rh-negative blood should be given if she is found to be Rh-negative.

Rh AND ERYTHROBLASTOSIS FETALIS

The concept of the relation of the Rh factor to erythroblastosis has remained much the same during the last few years. Over 95 per cent of all women who bear children with this disease are Rh-negative when tested with standard serum and by the various methods which are now in use either blocking or agglutinating antibodies can be demonstrated in the blood of practically all such women. A few instances have been reported in which low titers of antibodies have been found in the blood of a mother of an Rh-positive child who failed to show evidence of erythroblastosis. Such a condition must be rare and the data so far presented are relatively meagre.

A or B blood factors when present in the offspring and absent in the mother have occasionally been considered the cause of erythroblastosis. It is believed that the maternal production of abnormal anti-A or anti-B immune bodies may be a response to stimulation by the cells of the fetus. In many of the cases thought to be due to the antigenic effect of A or B substances the diagnosis of erythroblastosis has been open to question.

The presence of one of the Hr blood factors in the fetus and its absence in the mother has also been established as a cause of immunization and resulting erythroblastosis.

The reason for the variation in the clinical manifestations of erythroblastosis is still not known. Although the duration and degree of

maternal immunization are commonly considered the factors determining the severity of the disease, other unknown conditions are probably of more importance. It has been suggested that a difference in the protein constituents of the blood of the infant before and after birth may be responsible for the frequent increase in symptoms following delivery—that the newborn infant possesses proteins which facilitate antibody-antigen reactions that are lacking in the fetus. It has also been suggested that erythroblastosis characterized by jaundice immediately after birth is an entirely different disease from that in which the jaundice reaches its height at three or four days of age and the importance of Rh immunization as the common cause of all forms of erythroblastosis has been questioned. This has not been adequately supported and existing data indicate that it is probably incorrect.

The names erythroblastosis and erythroblastosis fetalis as inclusive terms for the disease produced by antigen-antibody reaction in the fetus and newborn have been subjected to criticism since the discovery of the Rh factor. Hemolytic anemia of the newborn has been accepted by many investigators as a preferable term and thus, in turn, has been changed to congenital hemolytic disease in some publications. The name makes little difference so long as it is realized that a specific disease entity does exist which has a uniform etiology and in which the various clinical manifestations are so closely integrated that it is impossible to produce more than an artificial separation. The terms (a) fetal hydrops, (b) icterus gravis, and (c) anemia of the newborn are practically synonymous with (a) extreme, (b) severe to moderate, and (c) mild forms of erythroblastosis or congenital hemolytic disease. There has not as yet been any evidence brought forth to prove that any specific type of antibody is associated exclusively with any form of the disease.

The treatment of erythroblastosis remains the same as when it was first shown that Rh negative cells survive longer in the circulation of the affected infant than do Rh positive cells. Treatment is symptomatic; if anemia exists intravenous transfusions must be given. If anemia does not exist the addition to the circulation of unneeded blood appears to increase the rate of cell destruction, further to overtax elimination by the liver and to increase the possibility of brain injury. A few investigators have reported finding Rh positive cells satisfactory for purposes of transfusion, but at the present time the evidence supports the use of Rh negative cells for the first few weeks of life in preference to Rh positive cells. No medication has been found of value in the early stages of the disease.

No methods have been discovered by which maternal immunization may be prevented or the degree of immunization lessened after the immune state has once been established. No method of protecting the fetus against the effect of maternal immunization during its intrauterine

life has been evolved. Early delivery by cesarean section has a theoretic therapeutic value, but the results for the most part have been disappointing. Transfusion either through the umbilical vein or through some other vessel immediately after delivery may in rare instances be life-saving and preparations for such a procedure should be made in advance of delivery when a woman has previously given birth to a baby with proven erythroblastosis. Exsanguination transfusions of the baby immediately after birth appear to have been followed by excellent results in a few cases but the technical difficulties encountered make it impractical for general use.

Lengthening the interval between pregnancies does not seem to be of value in preventing the disease.

SUMMARY

All human red blood cells contain one or both varieties of each of three pairs of antigens, all cells will consequently possess Rh' or Hr' or both and Rh₀ or Hr₀ or both and Rh'' or Hr'' or both. Only one member of each pair is present in a single chromosome and eight possible combinations exist. With two chromosomes twenty-seven different combinations are theoretically demonstrable.

Maternal immunization may be evidenced by the presence of either agglutinating or blocking antibodies.

No means of preventing immunization of susceptible women during pregnancy or of preventing the development of erythroblastosis in an Rh-positive fetus conceived by an immunized woman has been found.

The treatment of erythroblastosis in the infant after birth is symptomatic. If anemia exists, blood transfusions using Rh-negative blood of compatible group should be given immediately.

UNUSUAL CLINICAL MANIFESTATIONS OF CHRONIC HYPOPARATHYROIDISM

HERMAN A. LEVY, M.D. *

THE introduction of dihydrotachysterol¹ has facilitated the treatment of parathyroid deficiency. Most recent studies² concerned the specific property of this derivative of irradiated ergosterol of raising the blood calcium level, the efficacy of which in hypoparathyroidism is no longer questioned. The diagnosis of hypoparathyroidism, however, may often be overlooked because of the tendency of the examiner to expect muscular tetany. Acute hypoparathyroidism, almost always a state of tetany complicating a thyroidectomy, is usually mild, transient, easily recognized and just as easily controlled. This is not true of chronic hypoparathyroidism, which usually follows a thyroidectomy but may appear spontaneously, varies greatly in severity and often shows a larval or latent tetany. Until the use of dihydrotachysterol it frequently defied all attempts at proper therapeutic control.

The condition of a number of patients who have attended our metabolic outpatient clinic over a period of years was initially unrecognized because tetany was not manifest or the main or presenting symptom was not especially suggestive of parathyroid deficiency. The following case studies present unusual manifestations of chronic hypoparathyroidism, occurring after a thyroidectomy.

Case I. Original Diagnosis of Stricture of the Esophagus, Cause Unknown with Suspicion of Carcinoma, Recognized at Esophagoscopy as Spasm

E. G., a white woman, aged 40 was referred in December 1943 by her private physician to our outpatient clinic for diagnostic esophagoscopy because of a stricture of the esophagus as shown by x ray studies. At esophagoscopy a normal esophagus with spasm was found and further medical study was suggested to rule out hypoparathyroidism. The patient had a thyroidectomy at the age of 17 for thyrotoxicosis. Not long after and periodically since the operation she experienced spells of "nervousness" which on further questioning were described as tenseness in the arms with clenching of the hands and a general feeling of fatigue and weakness. For three months before admission, she began to experience substernal pain associated with eating and difficulty in swallowing food and finally consulted her physician. A ray examination revealed a spasmodic stricture of the esophagus (Fig. 38).

Physical examination revealed a pale, undernourished white woman, tempera-

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ture 98, pulse rate 88, blood pressure 125 systolic, 80 diastolic. The hair and skin were somewhat dry and coarse. There were no abnormal findings in the pupils, lens or retina of the eyes. Both the Chvostek and Trousseau signs were strongly positive. Except for a thyroidectomy scar, there were no other significant physical findings.



Fig 38 (Case I)—X-ray evidence of spasmodic stricture of the esophagus in a woman with hypoparathyroidism

Laboratory data.

Urine negative for albumin and sugar

Blood hemoglobin, 65 per cent, erythrocytes, 4,350,000 per cu. mm, leukocytes, 6000 per cu. mm, normal differential count.

Blood Kahn test negative

Basal metabolic rate, plus 22, plus 3, plus 14 per cent.

Blood chemistry (all values in mg per 100 cc) total cholesterol, 203 and 192, total calcium, 4.4, inorganic phosphorus, 6.1, fasting glucose, 88, urea nitrogen, 10, creatine nitrogen, 1, total serum protein, 6.4, albumin, 4.4, globulin 2.0

The Q-T interval of the electrocardiogram (measured from the beginning of the QRS wave to the end of the T wave) was 0.40 second with a cardiac rate of 90

Daily treatment consisted of 1 dihydrotachysterol capsule (containing 2.5 mg of the drug), with 6 drams of calcium lactate powder taken orally. Improvement was rapid, all dysphagia disappeared along with the nervousness and tenseness that the patient complained of. Her

weight increased from 128 to 148 pounds. The blood calcium rose to 8.1 mg. per 100 cc., and the Q-T interval dropped to 0.32 second with a cardiac rate of 92. X-ray of the esophagus on September 9, 1945, showed no evidence of spasm. "The esophagus appeared entirely normal."

Although gastrointestinal disturbances due to muscular spasm in hypoparathyroidism are known and described as "nausea, belching, vomiting, diarrhea or spastic constipation and severe intestinal cramps,"³ there has been no report of esophageal spasm being due to a hypocalcemic state.

Case II. Marked Muscular Weakness Completely Incapacitating Patient for Many Years with Bilateral Lenticular Cataracts Diagnosed Originally as Congenital, and the Recent Added Complication of Pernicious Anemia

L. W., a white woman, aged 40, was first seen in the metabolic outpatient clinic in April 1937. A thyroidectomy had been performed in 1914 for a severely toxic goiter, the symptoms of exophthalmos, marked weight loss, heart palpitation, and nervousness being described by the patient. Immediately after the operation, and for five to six years thereafter, attacks of unconsciousness and severe muscle cramps completely disabled the young woman; her family was told that she could not recover. She described periods of loss of consciousness for as long as thirty minutes and almost continual cramping and stiffness of various muscle groups, producing such symptoms as dyspnea, aphonia, *accoucheur's* hand and stiffness of the neck, fingers and tongue. During this initial period, bed rest in the hospital or at home was practically continuous, treatment being symptomatic. Gradually there was a subsidence of the severe hypocalcemic symptoms and a cessation of the attacks of unconsciousness. From then (approximately 1920) till the time of admission, severe generalized muscular weakness had existed with periods of outspoken tetany interspersed with mild muscle cramping. About 1925 vision began to fail in both eyes. Bilateral cataracts were found, diagnosed as congenital, and operated upon in 1928 in Milwaukee, and again in 1929 in Chicago.

At the time of the initial examination, the patient's main complaint was the marked asthenia that prevented her from doing even light housework.

Examination showed a moderately pale, well developed woman, not acutely ill, with normal temperature, pulse and respiratory rate. Blood pressure was 110 systolic, 75 diastolic. Examination of the eyes showed a divergent strabismus with an opacity of the right lens, and capsular remnants in the left lens. The teeth enamel was hypoplastic, fingernails and hair were dry and lusterless. Chvostek's and Trousseau's signs were easily elicited. Except for the old thyroidectomy scar, no other abnormalities were found.

Laboratory data.

Urine negative for albumin and sugar.

Blood hemoglobin, 11.5 gm. (69 per cent); erythrocytes 5,030,000 per cu. mm. leukocytes 8,500 per cu. mm. normal differential count.

Blood Kahn and Wassermann tests negative.

Basal metabolic rate plus 8 and plus 11 per cent.

Blood chemistry (all values in mg. per 100 cc.): total cholesterol, 238; total calcium 4.44 and 4.9; inorganic phosphorus 7.2.

X-ray examination of the skull revealed no cerebral calcification as described by Eaton and Haines.⁴ Q-T interval of the electrocardiogram measured 0.40 second with a cardiac rate of 78.

During the first year treatment consisted of various preparations of vitamin D with calcium lactate. The blood calcium was raised to 6.5 mg per 100 cc on this management, but in November 1938 the patient was started on A T 10 orally. Since then she has taken 1 or 2 capsules (or their equivalent) of dihydrotachysterol daily, with the blood calcium being maintained between 8 and 9 mg per 100 cc. She was now able to work every day, and further eye surgery was carried out.

This patient had recurrent and severe tetanic seizures over many years, but it was the severe asthenia that brought her to the clinic. She had practically become inured to the muscular "stiffness."

Other authors who have noted this tendency to asthenia include Ketcham,⁵ "marked muscular insufficiency was noted in five adult patients," MacBryde,³ "general weakness and easy fatigue," Margolis and Krause's^{2b} and Cantor and Scott's⁷ patient complained of "general weakness," and Boothby's⁷ "of considerable muscular weakness." Lenticular cataracts are a well known complication of chronic hypoparathyroid states.

Early in September 1945 this patient complained of coldness and tingling in the legs and feet, but since her urine showed insufficient calcium output with the Sulzowitch reagent,⁸ these symptoms were interpreted as due to temporary latent tetany. On October 9, 1945, the blood calcium level was 8.1 mg per 100 cc., and the inorganic phosphorus 4.7 mg per 100 cc. The patient was not seen again until January 11, 1946, at which time the complaints of numbness and difficulty in walking made us realize we were not dealing with the usual symptoms of larval tetany. Neurological examination then showed a definite spastic gait and hyperactive deep reflexes, with a marked impairment of deep position and vibration sense in the lower extremities. An Ewald test meal revealed no free acid in the stomach contents. X-ray examination of the skull showed a fairly thick bone cortex, but again there was no evidence of calcification in the brain. Hematological studies of both the peripheral blood, and sternal bone marrow were typical of pernicious anemia.

Peripheral blood

Hemoglobin (electric photolometer), 9.9 gm

Erythrocytes, 2,640,000 per cu mm

Leukocytes, 7,200 per cu mm

Differential blood smear polymorphonuclear neutrophils, 67 per cent, eosinophils, 2 per cent, lymphocytes, 28 per cent, monocytes, 3 per cent

Definite evidence of anisocytosis, poikilocytosis and macrocytosis

Hematocrit (r), 34.0 per cent

Hematocrit (w), 0.8 per cent

Sedimentation rate (Wintrobe) 33 mm per hour (uncorrected), 18 mm per hour (corrected)

Mean corpuscular volume, 128 cu microns

Mean corpuscular hemoglobin, 37 micromicrograms

Mean corpuscular hemoglobin concentration, 29 per cent

Icterus index (normal 5-7½), 7.0 units

Sternal marrow aspiration (method of Dr L. R. Limarzi)⁹

Fat (yellow), 0.5 per cent

Fat (red), 0.5 per cent

Plasma, 61.0 per cent

Myeloid-erythroid, 5.0 per cent

Erythrocytes, 33.0 per cent

On treatment with liver injections, there has been gradual but definite improvement in the patient's condition. Last blood examination of May 24, 1946, showed hemoglobin, 10 gm, and erythrocytes, 4,490,000 per cu. mm.

The question arises as to whether the patient's long-standing asthenia had been caused by an unrecognized pernicious anemia. Against this is the fact that she had regained her strength and retained it for the past eight years, on treatment solely of the hypoparathyroid state. Also there had been no previous evidence of a macrocytic anemia on six previous careful hematological studies, although no sternal puncture had been done. A routine blood count done on December 2, 1944, showed a hemoglobin of 12 gm and an erythrocyte count of 4,440,000 per cu. mm.

The combination of chronic hypoparathyroidism and pernicious anemia must be rare, for Murphy,¹⁰ in his volume on Pernicious Anemia, does not mention the association, although he does feel that hypothyroidism and pernicious anemia occur together, possibly more commonly than reported.

There was no clinical evidence of postoperative hypothyroidism in this patient. She showed a normal basal metabolic rate on several occasions, and the total blood cholesterol was 238 mg per 100 cc—a high normal value. However, Freyberg's⁵ first patient had an achlorhydria, and Ketcham⁶ in the discussion of this same report stated that four of five of his patients who developed hypoparathyroidism after goiter operations showed an achylia on gastric analysis.

Case III Attacks of Unconsciousness, Mistaken for Epilepsy and Hysteria

V. T., a white woman, aged 27 years, first seen in May 1942, had undergone a thyroidectomy ten years previously. Almost immediately after the operation, she began to experience attacks of muscular twitchings and spasms of the hand muscles. Later preceded by mild muscle twitching more serious spells occurred, characterized by periods of unconsciousness lasting from ten minutes to about two hours at periods of several a week to once in several months. The patient described these spells as a daze or a nightmare, more common towards night when she was relaxed or lying down. Such characteristics of epilepsy as biting the tongue, frothing at the mouth and convulsions did not occur. The surgeon, who had done the thyroidectomy, recognized the causative factor and treated the patient with calcium salts and viosterol orally, and parathormone injections with fair symptomatic relief. However, after this surgeon died, several years passed before the patient came to the dispensary and, with only sporadic care, she again began to experience frequent attacks of loss of consciousness with no tetany. She consulted several physicians, one diagnosed epileptiform seizures, two others hysterical attacks, in spite of the patient's history.

Examination revealed a thin white woman with normal temperature, pulse rate 84, blood pressure 120 systolic, 80 diastolic. There was no evidence of opacities in the lens of the eyes. The hair and skin were dry and lusterless. Both the Chvostek and Trousseau signs were positive. A thyroidectomy scar was present, otherwise no abnormalities were noted. An electroencephalogram was not done.

Laboratory data

Urine, slight trace of albumen, no sugar

Blood: hemoglobin, 85 per cent, erythrocytes, 4,480,000 per cu mm, leukocytes, 7,800 per cu mm

Normal differential count.

Blood Kahn test negative

Basal metabolic rate plus 9 per cent.

Blood chemistry (all values in mg per 100 cc.) total cholesterol, 228, total calcium, 5.60; inorganic phosphorus, 5.75

The Q-T interval of the electrocardiogram was 0.38 second with a rate of 82.

Treatment consisted of oral calcium lactate and from 5 to 8 drops of the dihydrotachysterol solution in oil, 0.5 per cent (each 1 cc represents 5 mg. of the drug) or 1 capsule. The patient has had no further attacks or spells, the blood calcium being kept above 9 mg per 100 cc.

This patient was in the paradoxical position of knowing what was producing her seizures, but because her symptoms did not fit in with the usual picture of tetany, she was labeled hysterical or epileptic. Epileptiform convulsions occurred in eleven of Lachmann's patients¹¹ as well as in those of other authors^{2a, 12, 13, 14}. According to Taubenhaus and Engle,¹⁵ spells of complete unconsciousness are rare, and it is questionable if they occur because of hypoparathyroidism. These authors reported a patient with idiopathic tetany and epilepsy and thoroughly reviewed the literature regarding this association. However, other authors^{1c, 4, 16} did describe spells of unconsciousness, not epileptiform in nature.

Case IV. Bilateral Optic Papilledema, Developing in Uncontrolled Postoperative Hypoparathyroidism, Interpreted as Due to an Intracranial Lesion

F. A., a 38 year old white woman, was first seen in the surgical outpatient department in January 1943 for a large goiter producing dysphagia. There was no evidence, subjective or objective, of thyrotoxicosis. On May 12, 1943, a nontoxic nodular goiter was removed. On the first postoperative day the patient noticed a peculiar feeling like a tenseness in the face, nose, tongue and fingers, later replaced by actual cramps, the face feeling "like a board." Injections of parathormone produced immediate relief and were continued until discharge from the hospital. The patient was referred for further care to the metabolic outpatient clinic but did not attend until August 18, 1943. At this time she complained of a continuation of the cramps in the fingers and toes, stiffness of the face muscles and twitching around the mouth. On examination, the Chvostek and Trousseau signs were positive, and a diagnosis was made of postoperative hypoparathyroidism with latent tetany.

Blood calcium was then 6.4 mg per 100 cc and inorganic phosphorus 5.3 mg per cent. The urine was negative. The blood count was normal, and the blood Kahn test was negative. Treatment advised was three dihydrotachysterol capsules daily, and thirty-two 5-grain tablets of calcium lactate daily.

The patient discontinued her visits to the outpatient dispensary and received no further treatment until May 16, 1945, when she returned with complaints of marked weakness, and tingling and stiffness of various muscle groups. On examination the Chvostek and Trousseau signs were markedly positive. The blood calcium level was 6.6 mg and phosphorus 5.9 mg per 100 cc. The Q-T interval of the

electrocardiogram was 0.40 second with a cardiac rate of 75. Again treatment was started with a daily dose of 1 dihydrotachysterol capsule and 6 drams of calcium lactate powder. The dosage of A. T. 10 was rapidly increased to 3 capsules daily but with no real improvement. At this time the patient complained of a "clouding of vision" and was referred to the eye outpatient clinic. Examination there on June 11, 1945, showed clear media with elevation of the right disk of 2 diopters and the left disk about 3 diopters, both disks being edematous with blurred margins, no hemorrhages were present, and the periphery of both fundi were normal (Fig. 39 A). Vision was recorded as right 0.8 + 2 left 0.8 + 3. The diagnosis was bilateral choked disk, and the patient was referred to the neurological outpatient clinic.

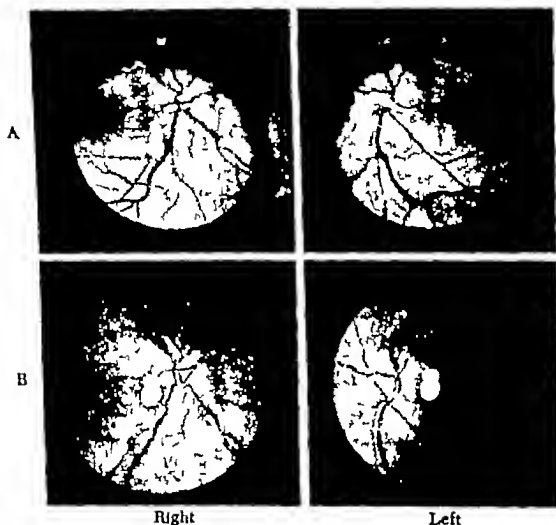


Fig. 39 (Case IV)—A, Papilledema in a woman with postoperative hypoparathyroidism B, After treatment

Between June and September of 1945, the patient was in the Illinois Neuropsychiatric Institute for various diagnostic procedures for a suspected neoplasm of the brain. During this time, the bilateral papilledema varied between 2 and 3 diopters with no impairment of the visual fields (Fig. 40), vision being recorded as 8/10 on the right, 10/10 on the left. There were no pathological reflexes, but a mild asymmetry of the face suggested a possible supranuclear right facial paralysis. X ray of the skull showed a rather large sella turcica measuring 17×18 mm., questionably within limits of normal. Spinal puncture with the patient well relaxed showed a pressure of 215 mm. of water, and normal spinal fluid with no abnormalities in cells or protein content. An electroencephalogram (Fig. 41) taken on June 20, 1945, was reported as: "Record shows good 10 per second activity in all leads. No seizure discharges, no forms of abnormal activity. Impression: Normal

electroencephalogram—10 per second No evidence of damage in accessible cortex”^o On July 25, 1945, a bilateral ventriculogram was made revealing moderately increased intracranial pressure, normal cortex and a somewhat larger left lateral ventricle than right There was no particular displacement or deformity

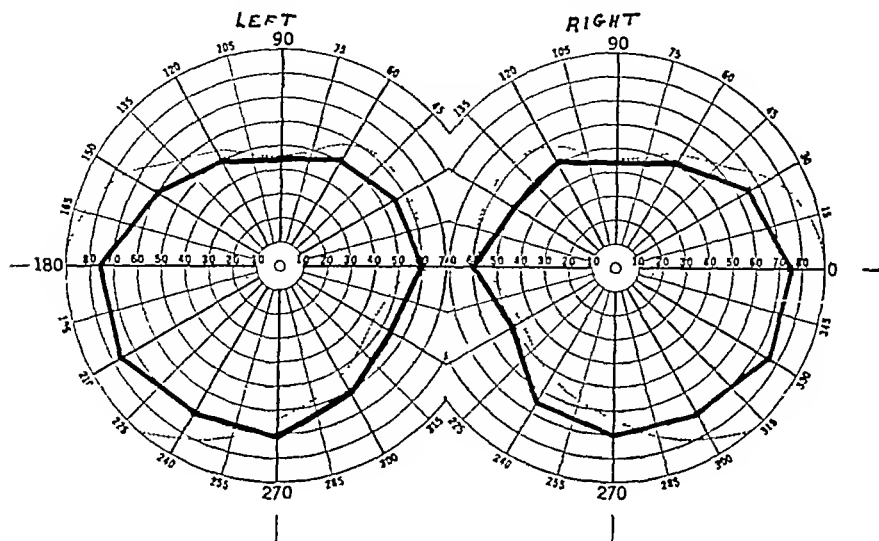


Fig 40 (Case IV)—No impairment is apparent in the visual fields

A neoplasm of the brain was suspected, with probable location in the midline, in or near the third ventricle or in the left cerebral hemisphere The patient was to be followed in the outpatient clinic and readmitted to the hospital for a subtemporal

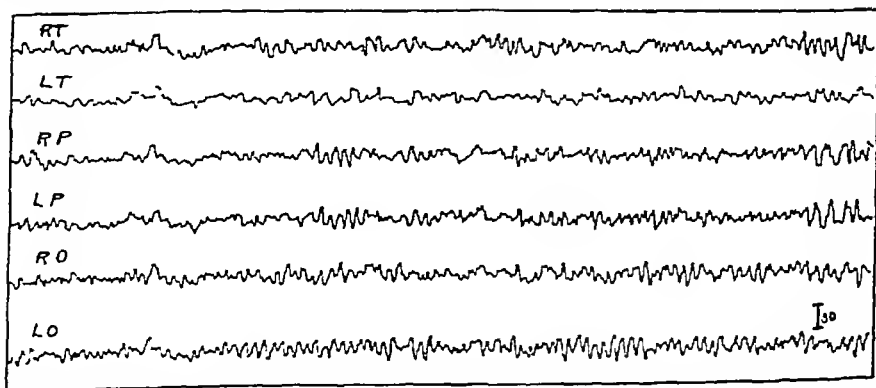


Fig 41 (Case IV)—Electroencephalogram shows good 10 per second activity in all leads No damage in accessible cortex is apparent.

decompression[†] for preservation of eyesight, or if further symptoms or localizing signs developed with increase or persistence of papilledema The electroencephalogram was repeated on November 26, 1945, again being normal with “no evidence of localized damage in accessible cortex.”

^o Electroencephalogram and interpretation courtesy of Dr Frederic A Gibbs, Illinois Neuropsychiatric Institute

The patient returned to the metabolic clinic on January 8, 1946, complaining mainly of "tightening and tenseness" of muscles of face, hands, chest and abdomen. Her eyesight with glasses had not become worse, visual fields were recorded on October 1, 1945 and again on January 7, 1946. There was still evidence of papilledema of both disks, although less than previously. The Chvostek sign was markedly positive. Blood calcium was 6.5 mg and phosphorus 5.2 mg per 100 cc. The patient was made to realize the importance of proper control of her hypocalcemia and became more cooperative. Treatment consisted of oral calcium lactate powder 6 drams daily, a low phosphorus diet,¹² and dihydrotachysterol in capsules, starting with 3 daily, and increasing to 6 daily. Blood calcium determinations were done weekly and the urine calcium level, as suggested by Albright,⁸ was determined every other day. Gradually the patient lost her muscular tenseness, the Chvostek sign lessened in intensity, the blood calcium level rose to 9.0 mg per 100 cc. and the papilledema receded greatly (Fig 30 B).

The occurrence of papilledema with uncontrolled hypoparathyroidism is certainly not unknown. Albrecht¹⁷ in 1924 described a patient with idiopathic tetany with papilledema and attacks of unconsciousness and was able to find nine other case reports in the literature. Barr, MacBryde and Sanders¹⁸ reported two more patients, one postoperative, the other with idiopathic tetany, both with attacks of unconsciousness, increased intracranial pressure and papilledema with subsidence of the papilledema on treatment with dihydrotachysterol. They stated "Neurologists and neurosurgeons who saw our second patient thought she had a brain tumor." They also mentioned a patient of Shelling and Goodman¹³ with the statement that "Bilateral papilledema was casually mentioned as an unexplained accompaniment of postoperative tetany." We feel our fourth patient is an example of the production of bilateral papilledema by an uncontrolled hypocalcemic state, the mechanism of which is still not understood.

DISCUSSION

Lachmanns¹¹ treatise presented a thorough and complete review of the usual symptoms and findings of hypoparathyroidism as it occurred in all such patients in Danish countries from 1934 to 1940. However, as well stated by Haines¹⁰ "In some instances the symptoms of parathyroid insufficiency are so mild as to be overlooked completely. In such cases, if the condition persists, recognition may be overlooked because of the absence of tetany." He then continued by listing such manifestations as fatigue and muscular weakness, gastrointestinal irritability, trophic disturbances as marked disturbances in growth of the nails, cataract, symmetrical regions of calcification in the brain, mental retardation, laryngeal spasm and respiratory stridor (if one vocal cord is paralyzed), and finally generalized convulsions. Blum²⁰ likewise attempted to describe some of the vague syndromes of latent or chronic tetany, adding "Marked emotional disturbances, especially crying spells without apparent cause," and such vague associated symptoms as palpitation, paresthesias, vascular disturbances, especially numbness of the

extremities and transient edemas Rose,²¹ in a later excellent review, made this statement "Chronic idiopathic hypoparathyroidism must be added to the many other organic disorders such as brucellosis, avitaminosis, hypothyroidism, et cetera, which must be ruled out in attempting to solve the problem of the patient with numerous vague and variegated symptoms" We also feel that a hypocalcemic state can manifest itself in one of many unusual ways, and should always be suspected, especially in a thyroidectomized patient having vague or peculiar complaints

SUMMARY

1. Four thyroidectomized patients with unusual clinical manifestations of chronic hypoparathyroidism are reported

2. The presenting symptom in each patient was as follows (a) Dysphagia, with spasmodic stricture of the esophagus shown on x-ray, thought to be due to carcinoma, (b) marked asthenia producing invalidism, with bilateral lenticular cataracts previously called congenital in origin (recently developing pernicious anemia), (c) attacks of unconsciousness, incorrectly labeled epilepsy and hysteria, (d) clouding of vision due to bilateral papilledema, thought to be due to a cerebral neoplasm.

3. Treatment consisted of dihydrotachysterol and calcium lactate powder orally, with a low phosphorus diet.

4. Some of the less well known and less obvious syndromes of chronic hypoparathyroidism are described

5. A hypocalcemic state should be suspected in any unexplainable syndrome affecting a thyroidectomized individual.

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SYMPOSIUM ON DIABETES

INTRODUCTION

ELLIOTT P. JOSLIN, M.D., F.A.C.P.*

THIS issue of *The Medical Clinics of North America* is dedicated to the subject of diabetes in recognition of the growing importance of the disease to all physicians. For today it is quite true that when a recently diagnosed diabetic, with onset of his disease under 30 years of age, enters the office, it means that the physician will have a patient to treat for as long as he remains in practice. In this number is brought together the experience of many authorities on diabetes. No physician, whether he treats many or few patients with the disease, would wish to give a clinic before students, a talk before a medical society or an interview with his patients without familiarizing himself with the views here expressed. Although not necessarily agreeing with all the opinions of the various authors, I believe that this symposium portrays more forcefully than hitherto the orthodox treatment of the disease.

The awakening of the people of the United States to the diabetic situation is still in its early stages. Only last year the United States Public Health Service entered the field in conjunction with the Commission of the Blind of the State of Massachusetts. Together they are conducting a study of the frequency of diabetes among the 6400 blind individuals in the State. In Oxford, Massachusetts, a town with 5000 inhabitants, the United States Public Health Service is carrying on a diabetic survey, perhaps the most complete ever made in the world. Yet the inadequacy of medical care and medical planning

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for diabetics is everywhere apparent. Too little teaching on diabetes is given to students in the medical schools. In the hospital, arrangements for the differentiation of the care of the elderly diabetic, close to the end of his career, and the youthful patient, just at its beginning with a future before him of useful work, have not been economically planned or hardly envisioned. The one group usually requires custodial care for weeks or months, whereas the other either enters with an acute complication or is ambulatory and seeks to receive in a week's time a serious and systematic course of education to last him all his life.

Recently there were thirty-five diabetics on one floor of the hospital with which I am associated. Twenty-eight of these were above the age of 40, with an average age of 64 and an average duration of their diabetes of thirteen years, or within about one year of the total duration of diabetes of all my recent fatal cases within and outside the hospital. In contrast, there were seven others with an average age of 25 and a duration of four years. Since beds are no longer available for diabetics except in emergencies, more and more doctors must seek to establish nursing homes or do what they have done for years, but now perforce on a far more extensive scale, namely, treat them in their offices with special provisions for their education. This will require so much time that they must have assistance from nurses, secretaries and technicians, or even other diabetics. Hospital rates for the care of diabetics, even in the wards, are going up. We doctors must discover the way whereby the cost for their care can go down, because we know there are a million diabetics waiting to receive proper treatment. The reorganization of hospital care is urgent but no more so than the reorganization of our own medical offices. Teaching diabetics must be done, but besides doing it better ourselves, we must begin with the education of hospital trustees and medical school faculties.

Despite the mounting number of living diabetics in the country, I venture the prediction that soon we shall witness what is even now and then and here and there noticeable, namely, a declining mortality from the disease. How is this anachronism to be explained? Frankly, diabetic statistics at present are of little value. They are not only unreliable but give a false sense of improvement in our treatment of diabetes. Diabetics really have almost ceased to die of their diabetes although they die *with* diabetes. May I elucidate this statement? Formerly 63.8 per cent of our patients died of coma and that went on the certificate, rightly so, as a diabetic death. Today about 3 per

cent die of coma and that leaves some 61 per cent of deaths due to other reasons. To fill this statistical gap cancer has jumped from 1.5 to 8.9 per cent, and arteriosclerosis in its various forms from 17.5 to 67.4 per cent. Obviously these conditions are not diabetic deaths and so they elude the statistician. If we are to improve our treatment, what we should do is to record the causes of death of the many diabetics coming under our care so as to know of what they die. Indeed, one almost might say that a death from diabetes is no longer allowable.

A burning question in the treatment of diabetes and one propounded daily by patients and doctors is, "Does hyperglycemia harm the diabetic patient?" I know of no better discussion in the literature or more convincing summation of evidence bearing on this point than has been gathered together for this symposium by Dr. Henry T. Ricketts of the Frank Billings Medical Clinics and the Department of Medicine, University of Chicago. In his article he also refers to a fourth type of experimental diabetes, recently announced by Lukens and Dohan of the Cox Metabolic Institute in Philadelphia,* by which continued hyperglycemia, artificially caused in a cat, will lead to permanent diabetes at the end of two weeks with changes in the pancreas analogous to those produced by injections of anterior pituitary extract. The clinic by Dr. J. D. Boyd illustrates the harmful effects of hyperglycemia and discloses the sorry complications following uncontrolled diabetes in the child.

The diagnosis of diabetes is discussed by our recent welcome visitor from England, Dr. R. D. Lawrence, and also from a different point of view by Dr. Herman O. Mosenthal of New York. Dr. Alexander Marble calls attention to the less common meliturias. These articles are timely because one must evaluate carefully new statistics which are being gathered wholesale in various surveys.

Any insulin is good insulin, even wonderful if we hark back to the days when we were treating diabetes without insulin. Even now if we had only one kind we could adjust patients to it. The danger is that with the multiplicity of insulins both doctors and diabetics become confused. In a clearly written article, Dr. Arthur R. Colwell portrays the actions of the different kinds and describes the success which he has had with a two-to-one mixture of crystalline and protamine zinc insulin. He points out that nearly half of his cases may be treated without any insulin (a much larger number than occurs in the writer's group), that for half of the balance he depends

* Article accepted for publication by *Science*

upon protamine zinc insulin or globin insulin, but for the remaining 25 per cent his best results have been obtained with a two-to-one mixture of crystalline and protamine insulin. In a companion article, Dr Franklin B Peck presents the difficulties and successes obtained with a special insulin which has not yet been put on the market. His paper indicates the problems which the manufacturers face. This clinic is followed by that of Dr Martin G Goldner who tells us in simple fashion how to manage our diabetics who show unusual requirements for insulin.

Although the results of Dr Colwell and Dr Peck are heartening, may I add a word of caution. It is safest to use methods to which one is accustomed or expects to use for some time. Under no conditions should one keep changing the treatment of a single individual just because a few bad tests for a short period are hard to explain. Remember Dr Peck and Dr Colwell are masters of their art and with almost any kind of insulin they would attain success. Prescribe no unfamiliar method except with deliberation, care and painstaking study.

The experience of the Mayo Clinic with insulin imposters is not unique, but not before has a series of such case reports been published. The article by Dr Rynearson shows clearly how these complicated deceptions can be discovered.

The number of diabetics in this country and the world is among the unknowns. Mr Herbert H Marks of the Statistical Department of the Metropolitan Life Insurance Company has assembled recent statistics of diabetes and diabetics to answer this question. I am pleased that he mentions that one estimate for the United States is as high as a million. Personally I am convinced that this is no overstatement and is if anything an understatement. My hat is always in the ring to defend this thesis.

The growth of the American Diabetic Association is not yet fully appreciated, although the Twenty-fifth Anniversary exercises of the discovery of insulin held in Toronto in conjunction with the University of Toronto called attention to its activities. These are described in a brief paper by its Secretary, Dr Cecil Striker, who has vitalized the Society from its start.

Diabetics are living a long time and that is the chief reason why there seem to be so many of them. Our group some months ago had 237, out of an original 249 with onset in childhood, who had survived diabetes twenty years or ten times as long as our fatal childhood cases between 1914 and 1922. One always welcomes reports from other

clinics in which diabetic children have been treated for more than twenty years I feel definitely, and my opinion is shared by my associates, that the carefully treated and diabetically controlled young diabetic patient is the one in best condition after twenty years and this is based not on seeing children merely during their early years, but as a result of following their course until they are grown up. Our colleagues, who advocate free diets for children and disregard hyperglycemia and glycosuria, as long as acetonuria is absent, as yet have not published the status of their children after twenty years. In his clinic entitled, "Incentives to the Treatment of Diabetes Mellitus," Dr F D W Lukens emphasizes early and prompt diagnosis with aggressive treatment seeking remission (not cures) in those brought early under control. He writes, "Nevertheless, twenty five years after the discovery of insulin, evidence is beginning to appear that the degree of control has an effect on some of the late complications as observed in groups of patients. Deviations from the highest standard of regulation should be made wisely but with reluctance." I suspect that in composing this paper he had in mind the experiments his colleague Dohan and he were carrying on, which demonstrated that persistent hyperglycemia in a cat would cause diabetes.

Pregnancy in a diabetic is still unusual. Dr Priscilla White, with Dr Raymond Titus as obstetrician and Dr Warren Sisson as pediatrician, and their associates, have had a great many cases in the last ten years. They and the nurses working with them at the Faulkner Hospital constitute an unusual team. The details of their procedures have not been published, but I hope will appear during 1947. Therefore, when a pregnant woman who had been diabetic for twenty five years came from a distant city and her husband and her doctor asked whether it was safe for her to continue her pregnancy, I grasped the opportunity to ask Dr White to give an answer based upon her experience with similar cases. I knew such a paper would be worthwhile.

Acute complications are always arising in any group of diabetic patients. Such are described by Dr Garfield G Duncan and Dr William M S Ling.

Despite the practical unanimity of belief of the wise and scholarly in diabetes that alloxan is not the secret to the disease, I still hold the opinion that it reaches to the heart of the trouble and feel strengthened in this idea by the discovery of Cori and his associates that in all their experimental types of diabetes—pancreatectomy, injection of anterior pituitary extract, alloxan—hexokinase acts at the same point in the intermediary metabolism of carbohydrate. For this

reason I asked Dr C Cabell Bailey to write a paper upon the clinical aspects of alloxan diabetes in animals.

"Uneasy lies the head that wears the crown," and that is certainly true of a diabetic camp director Dr. Waskow is not such, but she has worked intimately with us for three years and particularly with Dr. White for three seasons in camps for diabetic children. This phase of diabetic care deserves attention because diabetic children ought to go to camp if for no other reason than that their parents be given a vacation. I think diabetic camps are but the precursors of vacation houses for older diabetics and of rest and custodial homes for the aged diabetic in the not too distant future. They are examples of the reorganization through which diabetic procedures must go to be efficient.

Dr Sprague recognizes the role of insulin in the treatment of diabetic coma and that all else is subsidiary, while emphasizing the need of replacement of fluid and of electrolytes His article includes various details in treatment which will be found helpful

Another article by Dr. Howard F Root on diabetic coma in the light of his previous publications on this subject might seem like piling Ossa on Pelion, but how could I help extending an invitation to him to write on this topic when I actually see before my eyes the results of his methods? The prophylactic education of our clientele and the early recognition of coma by doctors, who send in their coma cases to us, unquestionably keep our cases milder than in those institutions where the undiagnosed patient first learns of his diabetes on recovery from his attack of acidosis Nevertheless, the results achieved by Dr Root and his colleagues deserve attention How should they be changed to avoid the four fatalities among the last 188 patients admitted in coma?

The entrance of the United States Public Health Service into the realm of diabetes is noteworthy From personal association and observation I can assure both physicians and the public that the task is being admirably and tactfully inaugurated by Major Wilkerson who gives a brief review of this work

In the Modern Art Gallery in Munich, which I visited in 1938, there were many pictures, which to my nonartistically trained sense seemed good and bad The one which appealed to me most of all was entitled *Schwere Arbeit*—Hard Work. It depicted four draught horses drawing a loaded wagon up a long hill Each animal was doing his level best and the same expression was conveyed by the serious faces of the drivers walking alongside. I could not easily secure a copy, be-

cause it was a Hitler favorite. But as a result of persistent questioning I succeeded. It was hinted that if I visited a certain courtyard, crossed it diagonally and climbed several flights of stairs to a back room I might obtain a replica. To me it is the epitome of what is needed for diabetic progress today—hard work by everyone, patients, doctors, professors, hospital administrators, all pulling together the heavy load of diabetic treatment up the long hill toward the goal we are all striving to reach—the prevention, the amelioration and the cure of the disease.

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DOES HYPERGLYCEMIA HARM THE DIABETIC PATIENT?

HENRY T. RICKETTS, M.D. *

THERE has recently arisen in this country a school of thought which believes that the careful control of the blood and urine sugar in diabetes is unnecessary. This school has found its most eloquent expression in the writings of Tolstoi,¹ who states that he allows his patients to eat largely as they please, gives only enough insulin to prevent ketosis and dehydration and permits the excretion of as much as 100 gm. of glucose per day in the urine provided it does not lead to symptoms. These patients, he says, are apparently in just as good health after several years of such treatment as are those managed by time-honored methods. Disregarding for the moment the possibility that it is as yet too early to judge whether this sort of management will be harmful in the long run, or may even by now have resulted in undetected damage, it cannot be denied that, if proved innocuous, it would greatly ease the burden of both doctor and patient. Indeed, the idea is so attractive that it seems likely many physicians will be tempted to adopt it without due consideration of certain facts, old and new, which taken together may be interpreted as spelling "Caution—slow." It is the purpose of this article to marshal these facts before you.

THE ROLE OF THE PANCREAS IN DIABETES

The proponents of the school of "liberalism" state necessarily that hyperglycemia in and of itself is not harmful. This point of view is a bold departure from certain of the older teachings with which most physicians have been brought up, namely that sustained hyperglycemia may overstrain and exhaust the already inadequate islet tissue of the pancreas and, furthermore, that it may be responsible for the degenerative lesions of the blood vessels and other tissues which characterize many cases of long standing diabetes. These concepts, then, need to be re-examined in the light of recent allegations that they are not valid. The first question, however—that of whether hyperglycemia injures the pancreas—leads us at once to a prior question. To what extent is the pancreas involved in the pathogenesis of human

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diabetes? This is more than an academic matter, for if it could be established that the pancreas plays any role, great or small, in this connection, then we as physicians would be duty-bound to protect and restore that organ in our patients by whatever means we considered effective. Much of the evidence concerning this point has, of necessity, been derived from animals and can be applied to man only by inference, but clinical and pathologic observations have also had their part in the pendular swings of theory which have alternated between the pancreas and other endocrine glands as being the primary causative factor in the diabetic syndrome.

The experiments of Von Mering and Minkowski,² in which diabetes was produced in dogs by pancreatectomy, so influenced thinking on the subject that for years it was generally assumed that the disease in man must be of purely pancreatic origin. Eventually, however, as methods for measuring the sugar of the urine and blood came into wider use, it was found that glycosuria occurred commonly in conditions which involved other organs, particularly tumors of the hypophysis and of the adrenals, Grave's disease and some disorders of the liver.

Further discrepancies appeared in the pathology of the pancreas itself. Massive destruction of that gland by tumor or inflammation was not usually accompanied by diabetes and, conversely, postmortem examination of many patients dying with diabetes showed no histologic changes in the islands of Langerhans. Warren,³ in 1930, stated that in 27 per cent of 259 pancreases from diabetic patients the islets appeared entirely normal, while many of the remaining 73 per cent showed lesions of only slight or moderate degree, insufficient to account for the diabetes in the light of the fact that, as then known for the dog and as recently found for man, it is necessary to remove at least 90 per cent of the pancreas before permanent diabetes results. The possibility that changes in function may take place without being reflected in cellular structure has recurrently been raised but not proved.

In 1927 Johns, O'Mulvenny, Potts and Laughton⁴ reported the production of transient glycosuria and hyperglycemia in dogs by the injection of extracts of the anterior lobe of the hypophysis. Their results were confirmed a few years later in dogs by Evans and associates⁵ and in rabbits by Baumann and Marine.⁶ In 1930 Houssay and Biasotti⁷ reported that hypophysectomy in dogs previously made diabetic by pancreatectomy practically abolished the diabetic syndrome. Glycosuria could be made to reappear by the injection of anterior pitui-

tary extracts Houssay concluded that a pituitary factor must be present in all diabetes.⁸ The importance of the pituitary was fully brought out by Young,⁹ who in 1937 succeeded in producing permanent diabetes in normal dogs by the prolonged administration of crude anterior lobe extracts. Almost paralleling these developments in the role of the hypophysis was the work of Hartman and Brownell¹⁰ and particularly of Long and Lukens¹¹ on the adrenals. These investigators found that adrenalectomy ameliorated pancreatic diabetes in the cat just as did hypophysectomy in the dog. The converse of these experiments, the induction of diabetes by the injection of adrenal cortical extracts, was not accomplished in normal animals, but accentuation of the diabetes of partially depancreatized rats by the administration of certain fractions of adrenal cortical extract was achieved by Long and his co-workers¹² and by Ingle.¹³ Thus, there was good evidence that both the anterior lobe of the hypophysis and the adrenal cortex possessed diabetogenic properties of considerable potency.

Attention was redirected to the pancreas when Richardson and Young¹⁴ announced in 1938 that the injections of anterior pituitary extract which caused diabetes in dogs produced at the same time alterations of the islands¹ of Langerhans consisting, as judged by special staining techniques, first of stimulation of the beta cells, later "exhaustion" and finally hydropic degeneration, hyalinization and atrophy. In the next year Best, Campbell and Haist¹⁵ showed that the pancreatic glands of dogs made diabetic by this method contained less than 0.2 units of insulin per gram as compared with the value for normal dogs of 3.4 units per gram. In cats, Lukens and Dohan¹⁶ found that anterior pituitary diabetes could be produced only after partial pancreatectomy, but here too the development of the disease was accompanied by characteristic lesions of the islets in the pancreatic remnant. Thus it appeared that whenever diabetes was artificially induced in animals, the pancreas was somehow involved, a generalization which was given further point by the discovery of Shaw-Dunn and McLetchie¹⁷ that alloxan produces a highly selective destruction of the beta cells followed by full blown diabetes. On the human side, Scott and Fisher¹⁸ found that whereas the insulin content of the pancreas in non diabetic persons averaged 173 units per gland, in patients dying with diabetes it was less than 40 units. While insulin content does not necessarily bear a direct relation to insulin production, the fact that anterior pituitary diabetes in animals has been shown to be characterized by a marked decrease in pancreatic insulin with parallel histologic changes in the beta cells, suggests that insulin

content may afford some index of islet activity That sufficient damage to the pancreas of man causes diabetes has been demonstrated by the invariable appearance of the disease following total pancreatectomy¹⁹

In summary, no unequivocal answer can be given to the question of whether the pancreas is of prime importance in the pathogenesis of spontaneous diabetes In the rather confused picture, however, two significant facts stand out. One is that permanent diabetes has never been produced in animals without damaging the pancreas The other is that, while a considerable proportion of human cases show at autopsy insufficient involvement of the islets to explain the disease, there is about an equal number in which definite insular lesions are demonstrable even with ordinary histologic technics, and it is possible that with modern specific stains defects in the beta cells will be found in a higher percentage of cases It seems reasonable to conclude that the pancreas is in all likelihood involved to some degree, though perhaps not exclusively, in at least a large number of patients with diabetes mellitus

INJURIOUS EFFECTS OF HYPERGLYCEMIA ON THE PANCREAS

If the probable correctness of this conclusion be granted, we are now in a position to inquire into the question of whether hyperglycemia is capable of injuring the insulin-producing cells of the islets Again we must turn to animals for much of our evidence Here the pioneer experiments of Allen²⁰ on partially depancreatized dogs are so important that his summary of them is quoted verbatim

"1. After removal of sufficiently large fractions of the pancreas, dogs develop a severe diabetes, in which they show heavy glycosuria on meat diet and also during considerable periods of fasting The condition progresses steadily downward to a fatal end

"2 When the remnant of pancreas left in situ is slightly larger, a condition may be produced in which the fate depends on the diet. On meat feeding such a dog is free from glycosuria and remains so for months, eating his fill every day and maintaining full health and nutrition, with no sign of downward progress, but subcutaneous tests show that the dextrose tolerance is very low, and bread feeding readily produces glycosuria A return to meat diet stops the glycosuria, but if the bread diet and accompanying glycosuria are maintained for too long a time, the glycosuria then continues, even on meat feeding The diabetes thus produced is not inferior in severity to that resulting from simple removal of larger fractions of pancreatic tissue, and the downward course and fatal termination are similar

"3 When the pancreas remnant is still larger, glycosuria is absent on meat diet, and on bread diet may be absent or transitory. Such animals may remain in excellent condition indefinitely on bread diet, free from glycosuria or any downward tendency, but if sufficient sugar is added to the diet, glycosuria can be produced and maintained. After a period of such glycosuria, the animal reaches a condition in which it is glycosuric on bread diet. By prolonging the glycosuria on bread diet, the dog finally reaches the condition of severe diabetes, with glycosuria on meat diet and continuous downward progress."

The beta cells of dogs thus made diabetic showed the specific lesion of hydropic degeneration. It is apparent that if means are taken to induce and maintain glycosuria (which, of course, means hyperglycemia) in dogs with a lowered pancreatic reserve, irreversible diabetes results. The implications of these experiments led Allen to treat diabetic patients by undernutrition. It was assumed, of course, that diabetes in man was essentially pancreatic in origin and, thus being the case, that a low calorie diet would impose as small a burden as possible upon that organ and favor its restitution. It was clearly demonstrated that when a patient, who before such treatment could tolerate only a few grams of carbohydrate without glycosuria, was rendered sugar free by fasting and was then fed a gradually increasing diet, he eventually became able to take several times the amount of carbohydrate which had originally caused glycosuria without now losing any glucose in the urine. Most important from the standpoint of this discussion was the fact that the gain in tolerance so achieved would often be lost if, by reason of dietary excess, sugar were allowed to reappear in the urine in large amounts or for long periods of time. Thus, the adverse effects of hyperglycemia on the course of the disease in man were clearly evident, even at that early date.

Within the past ten years further observations have been made in animals which offer convincing support for the hypothesis that hyperglycemia is injurious to the pancreas. Jacobs and Colwell²¹ found that the constant injection of glucose intravenously in normal dogs for periods up to seven days led to massive hemorrhage into the anterior pituitary and pancreas, as well as intense hyperemia of the adrenal cortex. The levels of blood sugar attained were, of course, far higher than those occurring in spontaneous diabetes, but the fact remains that an excess of glucose alone was responsible for the lesions. Very recently Lukens²² has caused permanent diabetes in cats by the daily intraperitoneal injection of glucose over a period of several weeks. Young²³ in attempting to induce diabetes in dogs by injections of anterior pitu-

itary extract, was successful only when the animals were well fed, and found that starvation or undernutrition prevented diabetes in other dogs similarly treated. In the production of this type of diabetes it is necessary to administer large doses of extract daily for several days. The earliest abnormality to appear is an elevation of the blood sugar. Now if, during such a course of injections, *any procedure which will prevent hyperglycemia is instituted, diabetes does not ensue.* Quite as effective as starvation are low carbohydrate, high fat diets,^{23, 16} insulin^{23, 16} and phlorhizin²⁴. In the cases of insulin and phlorhizin, not only are they capable of preventing the disease under these conditions, but when they are given to cats within three months of the development of frank, pituitary-induced diabetes, the disease can be "cured." Biopsies of the pancreas in such animals have shown that the islets, which soon after the administration of the diabetogenic substance exhibit the typical hydropic degeneration of incipient diabetes, revert to a normal architecture under the influence of these measures. There can be no doubt that in such experiments the diabetogenic principle of the anterior pituitary destroys the islets of Langerhans, either by affecting them directly or by causing hyperglycemia which eventuates in the exhaustion of the beta cells. The evidence at hand points strongly toward the latter as the most important, if not the only, mechanism involved.

The effect of a high blood sugar in human beings is more difficult to evaluate. Because patients cannot easily be subjected to controlled conditions over long periods of time, we must depend chiefly on clinical experience for our conclusions. It is argued that many diabetic patients live for years with glycosuria and show no apparent ill effect. It will be granted, however, that in the first place, such patients are for the most part only mildly diabetic and, in the second place, our methods for determining whether deterioration has taken place are in many cases inadequate. Against this unsatisfactory group we may place certain patients who have been carefully observed during periods of good control and poor control. It was well known in the pre-insulin era, as pointed out earlier in this article, that tolerance for carbohydrate increased under dietary restriction. It is equally well known today that many patients who on first beginning treatment require small or moderate doses of insulin may, if well controlled, later discontinue its use or take more carbohydrate on the same dose and still remain sugar free. On the other hand, it is a common experience to find that patients in whom satisfactory control of the blood sugar has been well established and who then lapse from grace for some months

by overstepping the diet or omitting insulin, now require insulin permanently where none was needed before or must take permanently larger doses than those which formerly were adequate. It is difficult to escape the conclusion that in these patients hyperglycemia has been harmful. Conversely, that avoidance of hyperglycemia is beneficial has been most recently shown by the work of Brush.²³ This investigator treated thirty-nine children with diabetes of short duration by large, frequent doses of insulin sufficient to keep the blood sugar below normal for from three to four weeks. At the end of this time the patients were discharged from the hospital well controlled with an insulin dose of from two to eight units per day, about one third as much as that required by a group of comparable cases treated by other physicians in the orthodox manner. The present essayist can confirm the effectiveness of this treatment in the limited number of cases in which he has used it.

The arguments thus far presented have dealt with the question of whether hyperglycemia damages the pancreas. The evidence in animals indicates that both functional and structural injury to the beta cells may result if the blood sugar is allowed to remain high, certainly during the incipient stages of diabetes and possibly even after the disease has become fixed. The evidence in man, while not so definitive, points in the same direction.

RELATION OF HYPERGLYCEMIA TO THE DEVELOPMENT OF DEGENERATIVE COMPLICATIONS

What of the degenerative complications? Is their development related to the degree of control of the disease? This is perhaps the most important problem in clinical diabetes today, and our information is as yet too scanty to permit a satisfactory answer. While there is no doubt that arteriosclerosis, cataract, specific retinitis and intercapillary glomerulosclerosis occur more commonly in diabetics than in the rest of the population, this fact does not tell us what there is about diabetes that accounts for it. Is it the high blood sugar? The elevated serum lipids? Or may there be a common factor which produces both the diabetes and the complications as two branches of the same tree? A few recent observations in animals indicate that pancreatic diabetes, regardless of how it is produced, may give rise to the same types of lesions which are seen in long standing cases in man. Dragstedt²⁴ found arteriosclerosis in 15 per cent of his depancreatized dogs but in only 1.2 per cent of normal dogs. In these animals glycosuria was "fairly accurately controlled" with insulin but since they were being

observed for lipocarc deficiency their fat metabolism was abnormal a large part of the time Bailey and his associates²⁷ have noted the development of cataract in rabbits and rats made diabetic by alloxan but, though the rabbits received insulin, it is not stated how well the diabetes was controlled Foglia and Cramer²⁸ have observed that the incidence of cataract in alloxan-treated rats is proportional to the height of the blood sugar Finally, Lukens and Dohan²⁹ have reported intercapillary glomerulosclerosis at autopsy in a pituitary diabetic dog whose disease had been largely uncontrolled over a period of five years These laboratory observations, while suggestive, are not extensive enough to allow of general conclusions

The situation with regard to the diabetic patient is still very confused Degenerative lesions are seen in mild as well as severe diabetes, controlled as well as uncontrolled, the only common denominator predisposing to complications being apparently the duration of the disease When such statements are made, however, it must be with the realization that human material is very difficult to classify and analyze with any degree of accuracy The extent to which glycosuria is controlled in a given patient, for example, can be estimated over long periods of time only from the patient's own record of his urine tests, the reliability of which is seldom open to proof, and the glucose content of the occasional twenty-four hour specimen brought to the doctor's office may reflect only the previous day's abstemiousness, born of a subconscious desire to make a good showing

There is one clinical study, however, which deserves special attention because of the unusual opportunity which the investigators enjoy and utilize for the careful following of their patients Boyd, Jackson and Allan³⁰ have reported their findings in sixty-nine young adult patients previously under their care as children and later recalled to the hospital for examination Sixty of these had had diabetes five years or more and forty-two had had it for ten years or more The degree of control of the disease was termed good if hyperglycemia was fairly constant and glycosuria frequent or continuous though mild. Of the sixty-nine patients, seventeen had been of substandard height at the first examination, the average duration of the disease at that time being three and one-half years. Thirteen of these resumed the normal rate of growth under treatment Of the four who did not, three failed to follow instructions and one was apparently a pituitary dwarf At the terminal examination twelve patients were classified as dwarfs, no instances of this sort being encountered among well controlled children There were eleven cases of retarded maturation, none of

them occurring with properly controlled diabetes. Retinal hemorrhages were found in six patients and were related to periods of poor control. The six patients who had clinically demonstrable cataracts were all poorly controlled. Minor subcapsular opacities were found by slit lamp examination in approximately twenty cases, none of them fulfilling the criteria of satisfactory management. Such lesions were not present in the patients whose adherence to the prescribed regimen had been adequate.

Physicians who from their own experience are unable thus to correlate the incidence of degenerative complications with the degree of glycosuria must ask themselves in all honesty whether they really know the habitual extent of control in their cases, and advocates of the school of "liberalism" must wait another ten years before they can state convincingly that persistent hyperglycemia is innocuous.

SUMMARY AND CONCLUSIONS

The pancreas is probably involved to some degree in many cases of diabetes. Pancreatic diabetes in animals, except that produced by total pancreatectomy, can be prevented, ameliorated, or "cured" at various stages by measures which keep the blood sugar normal. In adult patients coming under treatment for the first time, maintenance of a sugar free urine usually leads to an increase in tolerance for carbohydrate and a decrease in requirement for insulin. In incipient childhood diabetes strict control of the blood sugar for several weeks results in a considerably lower insulin requirement than when the blood sugar is indifferently or poorly regulated. These facts indicate that if there is any way by which diabetes can be minimized or prevented from progressing, it must be by the avoidance of hyperglycemia.

That the lax control of the disease is responsible for the degenerative complications which characterize it has not been firmly established, but there is suggestive evidence in both animals and man that this may be the case. In the absence of proof to the contrary it is unsound and hazardous to abandon the goal of normoglycemia in the treatment of diabetic patients.

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ILLUSTRATIVE CASES

To illustrate the course of certain typical diabetic patients, I have chosen to review the records of three subjects who acquired their diabetes during their first decade of life, whom we have been privileged to observe recurrently until adulthood had been attained. For each of these patients, our records cover not less than twenty years during which each was living under some form of diabetic management.

CASE I—The first patient to be presented developed symptoms of diabetes mellitus a few weeks prior to her 9th birthday. Soon thereafter she came under the care of this department and we were responsible for her prescribed diabetic regimen for the next seven years. She was seen thereafter on occasion in other departments of the University Hospitals, at the time of her most recent examination she was 29 years old.

When first examined at the age of 9 years, this girl presented typical findings of uncontrolled diabetes with moderate acidosis. In other respects she appeared normal aside from some caries of her deciduous teeth and moderate undernutrition. The tuberculin test was positive, the girl's father was said to be tuberculous. The blood Wassermann test was negative. The girl was in the hospital for three weeks, at the time of her discharge she was of average height and weight for her age.

The regimen of diabetic management employed was typical of that used as a routine for all such patients in this department.¹ The girl's diet was prescribed in its entirety not only the amounts of protein, carbohydrate and fat, but in detail as to the specific foodstuffs and the amounts of each to be ingested each day. The nature of each menu was designed so that all nutritional requirements would be met in an optimum manner as fully as our knowledge would permit. The three daily meals were essentially isocaloric. Throughout the early years of this girl's supervision her diet was high in fat and low in carbohydrate, owing to our belief at that time that the insulin dosage was determined by the amount of potential glucose in the diet. In this high fat diet, the ratio between weights of protein, carbohydrate and fat was 7.9:21 respectively. Later when it had been proved² that insulin requirement is a function of total calories rather than of potential glucose, the girl's diet formula was changed abruptly to a protein-carbohydrate-fat ratio of 7:19:10 without change in the total calories, and her insulin requirement was not affected by the alteration.

Throughout her total period of supervision, this girl's insulin dosage

was prescribed with the goal of avoiding hyperglycemia and glycosuria as well as insulin shock in as great a measure as circumstances would permit. The day's dosage was distributed so that 40 per cent of the total was given an hour before breakfast, 20 per cent before lunch, 30 per cent before dinner and 10 per cent at 10 00 or at 12 00 P.M. By the date of discharge from the hospital the daily requirement had become essentially constant. The mother completed the finer adjustment of the dosage at home on the basis of the daily urinalysis. Thereafter, the patient returned to the hospital about three times each year, either as an outpatient or for admission to the wards. At such times the adequacy of the insulin dosage was established, and necessary diet readjustments were made. During much of the total period of supervision, the patient's sugar-handling function was maintained within limits approximating the physiologic state. Glycosuria was absent or was insignificant in amount and in frequency of occurrence. In addition to appraisal of the diabetic status, the periodic examinations included the examination of the teeth and of the structures of the eye.

The girl remained in excellent health throughout our total period of supervision, aside from chronic infection of the paranasal sinuses with some recurrent attacks of acute sinusitis. She had few episodes of acidosis or other diabetic complication. Her rate of growth was excellent, she matured normally and at the age of 15 years she was 65 inches in height. The total calories of her prescribed daily diet were altered progressively from a level of 2000 at the age of 9 to 3000 at the age of 13, then 2250 thereafter. Meantime her daily insulin requirement progressed from an initial level of 30 units to a total of 80 units when she was 16 years old. On occasions of acute sinus infection, her necessary daily dosage rose for short periods to as much as 120 units.

At the age of 16 years this girl was the picture of health. Her blood pressure was normal and no abnormality was discernible in the optic lenses or the fundi. Her teeth were free from any degree of caries or of fillings.³ She was happy and wholesome, and gave no emotional evidence of harm from her regimentation. All of our records indicated that this patient had adhered to our prescribed regimen with respect and determination.

The patient had no further medical supervision for the next five years. During that time she lived away from home and learned to compromise between the exacting regimen we had imposed and that obtainable through the public facilities for diet control. She did not test her urine frequently, and when tests were made glycosuria was the rule. When seen in the Department of Internal Medicine at the

age of 21 years she had some edema of the ankles, and a small retinal hemorrhage typical of diabetic retinopathy was discovered. She was restored to diabetic equilibrium with difficulty at that time. Her technic of diabetic control remained much less exacting thereafter than we believe is desirable, but she avoided any notable ill effects. The retinal changes did not progress. At the age of 27 years she was hospitalized because of an intractable trichomonas vaginal infection. Her daily insulin dosage at that time was from 80 to 100 units, taken as globin insulin. She became pregnant in her 28th year. Just prior to pregnancy her insulin dosage was 70 units daily, during mid- and late pregnancy the dosage was reduced to approximately half that value, with a caloric intake of approximately 2000. This regimen kept the patient comfortable and free from signs of ketosis or shock, but most urine specimens contained some amount of sugar. What her insulin requirement would have been throughout her third decade if her diabetes had been kept well controlled at all times can be only a matter for conjecture. When 29 years old she gave birth prematurely to a normal appearing male infant, who died six hours following birth as the apparent result of a subtentorial hemorrhage.

The initial record concerning this patient gave no evidence of a family history of diabetes. Later it was learned that a first cousin had developed that disease.

CASE II—The second patient developed symptoms of diabetes first at the age of 3 years. The paternal grandfather had been diabetic. No effort had been made to obtain diabetic equilibration during the first three years of the disease, and the child had frequent episodes of acidosis. She came to this clinic first at the age of 6 years. Two weeks previously she had had severe acidosis, and the local hospital care had not been sufficient to restore her earlier degree of well-being.

Our physical examination did not reveal much gross evidence of disease. Signs of moderate chronic upper respiratory infection were present, the teeth were markedly and extensively carious, and the girl was overweight for her age. She was of average height. Tuberculin and Wassermann tests were negative. The girl remained in this hospital for a month, during which time she received an appropriate diet and her insulin requirement was stabilized. During the interim her tonsils and adenoids were removed. At the time of discharge from the hospital her prescribed daily diet provided 45, 59 and 151 gm of protein, carbohydrate and fat, respectively. Her daily insulin dosage of 41 units was subdivided according to a percentage ratio as was described for the first patient. The record indicates that stabilization had not been completed at the time of discharge and that the pre-

scribed insulin dosage was moderately in excess of the child's needs. The mother was advised as to the manner of making the finer readjustments of dosage under some conditions, and was instructed to bring the child back to the hospital in a few weeks for validation of her status.

The patient did not return until seven years later. During the interval the prescribed regimen had not been followed in any degree. The child had eaten whatever she desired, and the mother had given 20 units of insulin twice daily without regard for the urine findings. When the urine occasionally had been tested, sugar always had been found. The child had had a ravenous appetite and the urine output had been great. For the past four years the vision had been poor. On many occasions the girl had complained of severe abdominal pain. Physical examination revealed marked retardation of growth, at 13½ years she was only 53½ inches tall, a value typical for a child four years younger. Her body weight, although low for a child of her age, was excessive for her height.⁴ The abdomen was protuberant and misshapen, largely because of a large and tender liver. No signs of approaching puberty were evident. The serum cholesterol level was 390 mg. The urine contained both sugar and acetoacetic acid. The customary regimen of diabetic management was reinstituted, and after a week had elapsed the liver no longer was tender. After twenty-two days the girl was discharged from the hospital. During her hospitalization period the diabetic state had come fairly under control, but the patient was not so easy to regulate as is the typical patient who is seen early in the course of his disease and who adheres to the prescribed routine regularly thereafter. Her discharge insulin dosage totaled 65 units daily and her diet supplied about 2000 calories. It was recognized that this diet allowance was inadequate for a child of her age even though it was acceptable for a child of her height. It was planned that the diet would be increased as rapidly as her absorptive capacity would permit.

During the next three months the prescribed regimen was approximated in some degree in the home. The mother arbitrarily discontinued the night dose of insulin. However, six months after discharge from the hospital the patient returned for examination, with complaints of headache and dizziness. Retinal examination, with marked right papilledema with flame shaped hemorrhages typical of diabetic retinopathy.⁵ Attempts again were made to reinstitute strict control of the diabetes evidently with some success. During the following eighteen months the liver gradually subsided to its normal size, the retinal abnormalities disappeared completely, and the girl grew six inches and gained 42 pounds. Menarche was established at the age of 15 years 3 months, the girl at that age measured 60 inches

in height. Her teeth were extensively carious, but the dental records indicate that little if any progression of caries had occurred during the previous two years.

Thereafter the pediatric department had no part in this patient's care, but records from other departments of the College of Medicine permit us to learn more concerning her subsequent course. At the age of 17 years she was referred to the Department of Internal Medicine by her home physician because of furunculosis of the vulva. The history revealed that after discharge from our service she had reverted to her earlier practice of noncontrol, she ate practically anything she desired, tested her urine infrequently, always found much glycosuria, and without reference to the findings maintained her insulin dosage essentially constant. Regular insulin was used. The patient declared that she had been taking four doses daily, with a total dosage of about 45 units. The diabetic state was not under control when she entered the hospital, but otherwise the patient showed no gross physical or functional abnormality. It was recorded that the disks and fundi were normal. The blood pressure was normal. The diabetes proved difficult to control, and the patient was not at all well equilibrated at the time of her discharge from the hospital.

When 20 years old, the patient was referred again to the University hospitals for diabetic regulation. She had become pregnant three months earlier, and her physician wanted the diabetic management adapted to meet the problems imposed by pregnancy. Her husband, incidentally, was also a diabetic patient. This young woman stated that she had followed her prescribed regimen of therapy with fair faithfulness during the previous two years, during which time she had had numerous minor insulin shocks which she attributed to her failure to eat regularly and to overactivity. Nine months previously she had traumatized her foot, and the area of ulceration had never healed completely. Laboratory studies in the hospital showed lack of diabetic control. Aside from the ulceration on the dorsum of the foot the remainder of the examination revealed no evidence of diabetic complication or sequel. At that time the patient was $61\frac{1}{2}$ inches tall. After three weeks in the hospital she was discharged practically aglycosuric, with a total insulin dosage of 60 units daily and with a dietary caloric equivalence of 2100. It was planned that she would return to the hospital later for her delivery but she did not. Correspondence two years later indicated that then she had had a subsequent pregnancy as well, and that both children were alive.

CASE III.—The third patient first developed symptoms of diabetes at the age of $3\frac{1}{2}$ years. A grandfather and an uncle had had diabetes mellitus. For a few years after the onset of the boy's symptoms he had

been under the care of competent internists but thereafter he received no systematic medical supervision. Because of recurrent glycosuria the mother had reduced the diet allowance prescribed for the boy when he first had been under medical care, for years he received insufficient food for his needs. Although according to the mother's statement, the boy had been of normal size as a child, he measured only $50\frac{1}{2}$ inches and weighed but $62\frac{1}{2}$ pounds when we saw him first at the age of 15 years and 4 months. The mother stated that he had grown but little since he was 10 years old, and only $\frac{1}{4}$ inch during the 14th year. Despite the small food intake and the daily use of from 30 to 40 units of insulin, the mother had not been able to keep the boy's urine sugar-free during the recent past. He had been acidotic on several occasions during the past two years.

The physical examination at the time of our earliest examination showed evidences of dwarfism and infantilism. The tuberculin and Wassermann tests were negative. The teeth showed minimal amounts of decay. The solid organs were not palpable and the blood pressure was normal. The optic lenses showed slight opacities which the ophthalmologist considered typical of congenital cataract and not of diabetic origin. The fundi were clear and the urine contained much sugar.

The diet prescribed for this boy supplied 98, 210 and 154 gm., respectively, of protein, carbohydrate and fat, it was much more liberal than any earlier diet regimen he had followed. Using our usual plan of therapy, which typically results in early stabilization of the patient who has but recently become diabetic, we were unable to establish normal levels of blood sugar or freedom from glycosuria. At no time during his course under our supervision did the urine remain consistently sugar free. As well as we could determine, the boy adhered with reasonable exactness to our prescribed regimen while in the hospital. Between the ages of 15 and 17 years he grew $6\frac{1}{2}$ inches and gained $26\frac{1}{2}$ pounds. When last seen his blood pressure was normal, he had minimal extent of tooth decay, and no abnormality of the fundus of the eyes was evident. Through correspondence we learned that at the age of 24 years he measured 60 inches and weighed 130 pounds.²

COMMENT

These patients exemplify the varied response which we have encountered with different levels of diabetic control. Many of our patients have adhered well to their prescribed regimen, have remained free from serious symptoms and tissue damage and have entered adult life in excellent physical and emotional condition. In contrast, those patients who have come to us first following years of inade-

quate management, or have failed to observe their prescribed regimen, are those who developed degenerative conditions and who experienced frequent severe complications. Growth has been unimpaired among those who maintained proper control. Many of those who did not follow good levels of management were below the average in physique both during the period of growth and as young adults.

Successful control of the diabetic patient is dependent in large measure on the thoroughness of the first program of stabilization. If attempts are made to compromise through the empirical use of insulin without means for accurate control of the diet or for diurnal urinalysis, even though the patient seems to make satisfactory symptomatic response to such therapy, nevertheless the diabetic state will become more resistant to effective therapy than if the patient is hospitalized at the earliest evidences of his disease and his condition is brought thoroughly under control. The state of mind as well as the physical condition of the patient will be modified by the thoroughness of the initial program of care. With planned regimentation from the start, the parent and patient will come to accept the situation and will condition their later attitudes accordingly. We have observed repeatedly that it is much more difficult to attain and maintain good diabetic control in the patient whose diabetes has been poorly managed for long periods than in the patient whose disease is of recent onset, or whose noncontrol has arisen because of recent infection.

We hold the following opinions as our basic philosophy regarding the treatment of the child with diabetes mellitus: (a) The prescribed diet should meet fully the needs for optimum nutrition, and should be prescribed fully as to ingredients as well as to amounts of protein, carbohydrate and fat; furthermore, the diet should be re-adjusted periodically to meet the changing demands of maturation. (b) The insulin dosage should be so regulated that glycosuria is avoided in so far as possible at all hours of the day and night, and the dosage should be revised sufficiently often to maintain this status. Either recurrent glycosuria or insulin shock are to be considered as evidence that the desired level of management has not been attained. (c) When infection or other intercurrent event occurs, the patient should be considered as potentially unstabilized, and special attention paid to his insulin requirements during such a period. A regimen which conforms to this basic plan should conserve the patient's innate metabolic capacities better than a less exacting routine.⁶

The proper regimentation of the diabetic child implies that the members of the household have insight as to the problem and its

immediate and ultimate goals, and are cooperative in all regards. It is easier to maintain long-term oversight and control of the diabetic patient in a good home than it is under other environmental conditions. New problems arise when the child leaves the parental roof for employment or to attend school. Such separation may demand that compromises be made between the desirable and the attainable. The greater the compromise, the greater hazard to the patient and his subsequent welfare.

One may question whether lessening of strict control of the diabetic state is fraught with danger in the young adult as it is with the child. We have observed that once early maturity has been reached, a patient tends to maintain an even course under given circumstances in much greater degree than was evident during late childhood and early adolescence. Once the hazards of growth are past, we believe that greater liberties may be condoned even though not encouraged. However, it will be noted that the first patient developed a retinal hemorrhage during her late teens as an accompaniment of her abandonment of strict diet control and its associated glycosuria. Such damage is better avoided than condoned.

The patients whose records have been reviewed were treated prior to the era of the slow acting insulins. Later studies with other patients have led us to conclude that protamine zinc insulin is poorly adaptable to the needs of the diabetic child.¹ It has not been possible to avoid undesirably wide fluctuations of blood sugar levels through the use of single daily injections of such insulins. Currently we are employing globin insulin together with regular insulin, and thereby we frequently avoid the need for a night dose. Unless techniques can be developed whereby the maintenance of good levels of blood sugar and the avoidance of glycosuria and shock can be assured, we feel it better to continue the practice of two or three daily injections, using regular insulin as the basis for therapy and globin insulin as a supplementary agent.

If the diabetic child's best interests are to be served, the attending physician must have available certain skills and facilities. If he lacks the requisites for the exacting care of the diabetic child, he should be reluctant to accept the responsibility for the care of such a patient. With such aids, employed with zeal and thoroughness, he can expect confidently that his young diabetic patient will make good progress with freedom from degenerative lesions so long as his diabetic state is kept approximately under physiologic levels of control.

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SYMPTOMLESS GLYCOSURIAS. DIFFERENTIATION BY SUGAR TOLERANCE TESTS

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THERE is no doubt or difficulty in the diagnosis of *severe* diabetes from the *symptoms*, the heavy glycosuria and the confirmatory hyperglycemia in one blood sugar estimation. But symptomless glycosuria is quite common and less easy to assess. It may be perfectly innocent and negligible or it may indicate the early stages of true diabetes and the differentiation is of great importance, not only for future health but for *economic and life assurance reasons*.

The term "glycosuria" merely indicates that a reducing substance is present in the urine. In clinical medicine alkaline copper solutions are used almost exclusively for this purpose, especially Benedict's solution. The only reducing substance of any pathological significance is glucose (dextrose) as it alone may indicate true diabetes. Several other reducing substances occur rarely and usually in small quantities, such as lactose, pentose and levulose, but their presence is entirely harmless. The presence of such a substance may be suspected from the finding of a constant and small reduction unrelated to food, whereas glucose varies directly with the carbohydrate eaten. These rare substances can be proved by special chemical tests described in any appropriate textbook, but they are often difficult to identify precisely when only traces are present. So, even after such identification, it is usual to investigate the carbohydrate tolerance by a glucose tolerance test, a procedure usually demanded by life assurance companies. Whenever the presence of dextrose (glucose) is established a glucose tolerance test is essential and the rest of this article will be confined to such tests and their meaning.

GLUCOSE TOLERANCE TESTS

There is no complete uniformity among different workers and in various countries in the detailed procedure adopted in carrying out a blood sugar curve (glucose tolerance test). I shall therefore first describe the procedure commonly adopted in England and my classification of various types of glycosuria arising therefrom. The blood sampled is capillary (arterial), not venous, the latter containing con-

siderably less sugar. Other procedures and classifications will be discussed later.

First a sample of *blood* is obtained in the fasting condition and at the same time a sample of *urine* is obtained, the bladder being completely emptied. It is usual to begin the test early in the morning when no food has been eaten since the previous evening but the result is the same if the test is begun any time four to five hours after food, for instance, at 2 P M after no food since breakfast, a time often more convenient. Then the test dose of glucose, 50 gm, dissolved in a glass of water, is drunk and every half hour for two or sometimes two and one-half hours the blood and a *simultaneous urine* sample are obtained for sugar analysis.

In this way a number of points are obtained to construct a blood sugar curve for comparison with the accepted normal. At the same time the relationship of glycosuria to glycemia is ascertained and the factor which determines this, the renal threshold, is discovered. The threshold may be defined as the blood sugar concentration (usually 170 to 180 mg per 100 cc) above which sugar appears in the urine and below which the urine is sugar-free. The level depends on the power of the kidney tubules to reabsorb the sugar filtered through the glomeruli. My classification of different types of curves and glycosurias is shown in Figure 42.

1 The *normal* response to a glucose meal is shown in curve *a*. Starting from a fasting level of about 100 mg per 100 cc (the range of normality in capillary blood is 70 to 120 mg) the blood sugar concentration rises rapidly to its highest level (as low as 100 and as high as 200 mg per 100 cc) in about half an hour, although sometimes the peak is delayed until one hour. It then falls nearly as rapidly and should be back at or below the fasting level in one and one-half to two hours, although this may be a little delayed in old age. As the usual renal threshold is not exceeded, all the half hourly urine samples are sugar-free. Slight departures from this standard of normality and other procedures of investigation will be discussed later.

2 *Diabetic* curves are also shown in the figure. The *mild* case (*b*) commences with a normal or near normal fasting level, but reaches its maximum later than normal, exceeds 200 mg per 100 cc and is *delayed* in its return to the fasting level. The renal threshold is exceeded and sugar is found in the urine examined at the end of one and one and one-half hours, but in no other sample. A *more severe* case (*c*) is also shown with all the diabetic features more marked, only the sample of urine in the fasting state being sugar-free. In a

really severe case, all the figures, even the fasting, are above this chart, and a tolerance curve is unnecessary and even harmful when symptoms of diabetes are present and one blood sugar estimation shows an indubitable hyperglycemia. Some doctors order blood sugar curves with glucose in order to follow the progress even of established insulin cases. This is harmful and unnecessarily alarming when figures

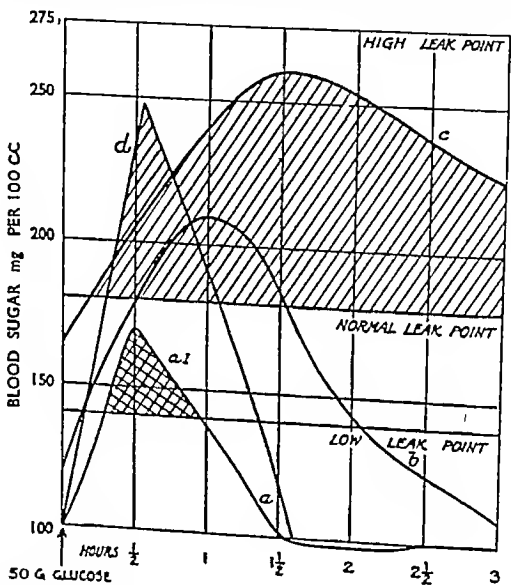


Fig 42.—Blood sugar curves in glucose tolerance test *a* Normal. *a.I*, Renal glycosuria. *b* Mild diabetes. *c*, Moderately severe diabetes. *d* Lag storage curve. Shaded area represents sugar in urine (Reproduced from "The Diabetic Life" 13th Ed by R. D Lawrence London A & J Churchill 1945)

of 400 to 500 mg. are obtained, and never does more than prove again that diabetes is present and obscures the state produced by the usual rhythm of diet and insulin

3 *Renal glycosuria* is due to a low renal threshold for glucose and not to an abnormal hyperglycemia in the blood sugar curve. The condition is sometimes called orthoglycemic glycosuria—a good name, and

sometimes diabetes innocens—a bad name. The condition is depicted in *aI* with a lowered leak point at 140 mg. Glycosuria is represented by the cross-hatched area and is present at the half and one hour urinary samples. But quite commonly this glycosuria, once started, persists to the end of the curve, as the threshold is commonly lower on the fall than on the rise of the curve. Sometimes the threshold is so low that glycosuria is present in the fasting state at a low normal blood-sugar (80 to 90 mg). Some authorities (Joslin and Marble) insist that this fasting glycosuria must be present before we accept with certainty the definition of renal glycosuria and the innocence of the condition. I cannot agree with this and think that renal glycosuria is proved whenever glycosuria occurs with a normal blood sugar curve, whether the urine contains sugar at the beginning of the test or not.

The condition is not rare and has been shown to be the commonest cause of glycosuria in selectees of the recent war, at least under 30 years of age. Sixty-five per cent of 800 cases of glycosuria in Army personnel investigated in London were proved to be of this nature. In most cases it is a life-long condition. It is inherited in some families as a Mendelian dominant characteristic so that half the children are affected, and it is a common temporary occurrence during pregnancy. It requires no treatment, does not develop into true diabetes and most insurance companies now accept a renal glycosuric as a first-class risk.

The term "normal" renal threshold often occurs in diabetic literature and introduces to my mind a falsehood in thought by implying that any departure from it is pathological. The accepted "normal" threshold between 170 and 200 mg per 100 cc is the usual *average* and departures below and above this average, quite common in normals and diabetics alike, points to no pathological change in the kidneys but merely a variation in the reabsorptive powers of the tubules producing no functional disability in the body's metabolism.

Certain pathological conditions do change the threshold, nephrosclerosis and circulatory failure in an upper direction, and phlorhizin and heavy polyuria in a downward direction. But the wide variations from the average, some as extreme as from 50 mg to 300 mg blood sugar concentration, imply no stigma of disease or impaired function.

4 *Lag-Storage Curve—Oxyhyperglycemia*—In some individuals glycosuria after certain meals is explained by the type of curve shown at the figure *d* and called by Maclean in 1920 the "lag-storage curve"—a poor name. From a normal fasting level the blood sugar rises rapidly after glucose to over 200 or even up to 300 mg per 100 cc but returns equally *rapidly* to the *fasting level in normal time*. Glycosuria occurs

in urines voided at one-half, one and perhaps one and one-half hours if the threshold is normal. If *venous* blood is used for analyses, as has been usual in America, this arterial hyperglycemia is missed and hence the condition is not described in the standard textbook (Joslin) The condition is not rare, occurring in 7 per cent of my glycosuric patients, but is far less common than renal glycosuria, under which category *oxy*-hyperglycemic cases will be classified from the results of venous blood analysis This type of curve is common in quick-emptying stomachs, after gastroenterostomy and the administration of glucose direct by duodenal tube and I expressed the view that its occurrence (Brit M J, 1 526, 1936) is due merely to rapid intestinal absorption and not to any defect in carbohydrate metabolism This has since been confirmed by O. K. Evensen (Acta med. Scandinav. supp 126, 1942) who, however, omits any reference to my paper I have suggested the name *oxyhyperglycemia* ($\sigma\chi\alpha$ = sharp, steep) to describe the sharp, bayonet shaped curve

The above are the four categories into which blood sugar curves can be classified and upon which clear-cut opinions for life assurance and other purposes can be based. There are, however, several other factors which disturb the normal curve and which must now be mentioned

Pseudodiabetic Curves.—Several conditions produce curves in normal people identical with the mild diabetic curve *b* and must be excluded before such a curve be taken to indicate mild or commencing diabetes mellitus requiring treatment These conditions are

1 *Toxic and septic conditions*, acute or chronic. I have seen many patients condemned to diabetic treatment from neglect of this fact, whose tolerance became normal when such conditions as purulent sinusitis and the like were cleared up A raised sedimentation rate may point to an obscure infection.

2 *Other endocrine disease* (a) thyrotoxicosis, (b) hyperpituitarism, (c) chromaffin suprarenal tumors

3 *Old age*, when carbohydrate tolerance is commonly reduced and where the blood sugar curve may show slight hyperglycemia and a slow return to normal

4 *Obesity*, where the curve is often abnormal but returns to complete normality on adequate reduction of weight. Whether the disturbed curve is an indication of commencing diabetes or not is a moot point.

5 *Precious starvation or carbohydrate restriction*, when ketonuria is often present. I always test the fasting urine at least for ketone

bodies The curve becomes normal after a week's full diet It is therefore essential that the patient should be on a full carbohydrate diet for at least a week before a diagnostic tolerance test

6 *Liver disease, especially hepatitis*

In the absence of the above complicating conditions, slight abnormalities in the glucose tolerance test occasionally occur which leave us in doubt and these will be discussed later In the meantime I shall consider different procedures employed by other workers for diagnostic purposes

Amount of Glucose and Duration of the Test.—Most workers in America give more than 50 gm of glucose, mostly 100 gm, and carry on the test for three hours Others employ the refinement of giving 1 gm per kilogram of body weight so that the dose varies from 40 to 100+ gm One hundred grams of glucose produce in a few patients a delay of the return to the fasting level from two to two and one-half or three hours, but most have a similar curve which returns to normal in two hours within wide limits of the oral dose We know that both after 50 or 100 gm, glucose is still present and being absorbed from the gut and the fall in the curve is not due to the end of absorption. I would not consider a blood sugar concentration as proving diabetes if it failed to return to the fasting level until three hours, but I would regard it as suspicious On the other hand, if the two hour figure is normal I should report a nondiabetic condition with confidence Dogmatism and certainty are required by insurance companies and patients For this reason I consider the normal two hour and fasting figure as the deciding levels in a confident opinion excluding diabetes

Arterial and Venous Blood.—Arterial (capillary blood from finger or ear is the same) contains more sugar than venous blood as the tissues abstract glucose as the blood passes through In the fasting state the sugar concentration is much the same but at the peak of sugar absorption, the difference between arterial and venous blood is usually 20 to 30 mg and sometimes 50 to 70 mg per 100 cc. This must be taken into account and explains different standards and classifications by different workers Thus the upper standard of normality would be 170 mg in venous with a corresponding 200 mg in arterial blood. It also explains why oxyhyperglycemia (type 4 curve) has not been described in America where, until recently at least, venous blood has been mostly used

Different Blood Sugar Methods.—There are various methods in clinical use (Benedict, Folin-Wu, Hagedorn-Jensen), and all give

figures sufficiently close to give a comparable standard. It should be realized, however, that all these ordinary methods estimate on the average 15 to 20 mg per 100 cc reducing substances other than glucose (mainly glutathione) and so a reading of 100 mg. per 100 cc. is only about 80 mg. of glucose and a figure of 20 mg per 100 cc. (in hypoglycemia) connotes a total absence of glucose from the blood.

Exton Rose Procedure (Am J Clin Path., 4 381, 1934) —This test, shorter in time than the above routine procedure, seems to be becoming increasingly popular in the United States, but is not used in other countries. After the fasting blood sugar and urine test, 50 gm of glucose are drunk and another blood sugar and urine collected after thirty minutes, when another 50 gm of glucose is given and the test concluded by a blood sugar and urine estimation in another thirty minutes. Here the test ends at one hour. Any investigation of the downward phase of the curve and accompanying glycosuria is omitted.

The criteria of a normal response seem to be that (1) the fasting blood sugar is under 120 mg. per 100 cc., (2) the blood sugar concentration at one hour should not be 10 mg above the half hour figure and should not exceed 160 mg per 100 cc., and the urine should be sugar free. Admittedly a high fasting level in addition to a really high figure at one hour gives conclusive proof of diabetes, but hardly more than an isolated estimation in relation to fasting or postprandial conditions. As a reliable procedure of investigation of symptomless glycosuria it is open to the following serious criticisms.

- 1 After a single dose of glucose, the sixty minute blood sugar is not infrequently higher than the thirty minute figure in the normal individual. It should be remembered that the intestine one hour after a glucose drink is still full of unabsorbed sugar and the effect of an added 50 gm at thirty minutes is probably negligible. The test is vaguely reminiscent of the Staub Traugott* procedure where the second dose of glucose is given after two hours when the blood sugar of the normal person has already returned to normal and is little raised by the second dose, whereas the diabetic blood sugar mounts higher after the second dose.

- 2 The to me, all important evidence of the fall of the blood sugar is completely missed.

- 3 The prolonged investigation of the relation of glycemia to glycosuria, i. e. clear evidence of the renal threshold and renal glycosuria, is obscured.

* Biochem. Ztschr 115-93 1921 Klin. Wchnschr., 1 892, 1922

4. The type of curve I have described as innocent oxyhyperglycemia would be classed as diabetic.

I can see no logical justification for this short-cut procedure and find that one blood sugar estimation, considered in relation to carbohydrate feeding or fasting, is almost equally conclusive or inconclusive, in the diagnosis of symptomless glycosuria.

Intravenous Glucose Tolerance Tests.—An intravenous technic is also employed to assess sugar tolerance after the infusion of usually 25 gm of glucose into a vein. This produces in normals an immediate hyperglycemia (300 to 400 mg per 100 cc) with accompanying glycosuria and a prompt return to the fasting level in about one and one-quarter hours. The technic has merits both as a diagnostic and experimental procedure but presents technical difficulties as a routine test. The glycosuria, which is almost constant near the beginning of the test, obscures the appreciation of renal glycosuria, and glycosuria caused by rapid absorption from the intestine (oxyhyperglycemia) is completely missed. As a method of investigating symptomless glycosuria it is far inferior to oral administration.

The *terms* and definitions I have used are clear enough, I hope, but others occur in the literature of quite uncertain meaning. I take particular exception to the phrase "alimentary glycosuria" whose meaning is vague though it implies that sugar is passed only after food. I should say that "alimentary" sugar can be proved to be due to one of the three conditions described and can be definitely categorized and should not be left vague and meaningless. I should like to see the term disappear from medical literature. I am not concerned here with odd temporary glycosuria caused by trauma, anesthetics and other easily noted factors, but with glycosurias in the healthy physically normal state of life. I should add that I refuse to give an opinion on a doubtful curve without knowing the condition of the patient in regard to general health, obesity, infections and other factors, and the detailed conditions under which the tolerance test is carried out.

DOUBTFUL GLUCOSE TOLERANCE TESTS

Let me repeat that if the fasting blood sugar is normal in a normally fed person and has returned to normal by two hours after a test dose of glucose we can and should declare the case nondiabetic whatever the intervening glycemia and accompanying glycosuria. I have never had cause to regret this ruling though obviously a few renal glycosurias in hundreds will develop diabetes by the law of averages. But a few cases occur in which the curve cannot be passed

as normal on the above criteria and in which the factors causing "pseudodiabetic" curves are not obvious and yet the curve obtained is so nearly normal that one hesitates to classify the condition as even potentially diabetic. In such cases I repeat the curve after two weeks of high carbohydrate diet and often obtain a different result which leaves no doubt for or against diabetes. If this second curve is still doubtful, I postpone decision and repeat the curve in three or six months, full diet being maintained and the fasting urine being tested occasionally to make sure that the glycosuria is not rapidly increasing I should mention that I see a few individuals who, even on full diet, produce traces of ketonuria in the fasting condition, pointing to a state of slight starvation likely to invalidate the curve (see above) I have found it useful to give 30 gm (1 ounce) of glucose two hours before the actual standard glucose test is begun and this sometimes turns a doubtful into a nondiabetic curve by a modification of the Staub-Traugott procedure

SUMMARY

The diagnosis of symptomless glycosuria by the glucose tolerance test is discussed and dogmatic standards for life assurance and other purposes are laid down. If the fasting blood sugar is below 120 mg per 100 cc. and has returned to this figure at two hours after 50 gm of glucose, we can classify the case with confidence as nondiabetic whatever the intervening concentration of glycemia and the accompanying glycosuria. Two innocent types of glycosuria, renal and oxyhyperglycemic glycosuria, are pointed out and discussed.

INTERPRETATION OF GLUCOSE TOLERANCE TESTS

HERMAN O MOSENTHAL, M D , F.A.C.P *

IN 1925 a clinic on "The Interpretation of Sugar Tolerance Tests" was presented in *The Medical Clinics of North America*.¹ This topic is of urgent importance because, unless there is a means for an accurate diagnosis of diabetes, many persons will be subjected needlessly to the inconvenience of treatment and many will be denied the privilege of life insurance. Since 1925 further studies have been carried out and it is on those that the present clinic is based. Although these and the attempts of many others to formulate a final positive diagnostic test for diabetes have failed in creating a procedure that possesses the specificity of a Widal or a Wassermann reaction, yet some progress has been made and is the theme of this clinic.

TECHNIC OF GLUCOSE TOLERANCE TESTS

Status of the Patient—The patient should be in the fasting state. The morning hours before breakfast have been universally accepted as the time for the performance of the glucose tolerance test. For the sake of evaluating present and past statistics this seems worth continuing, even though the test dose of glucose given to a person who has received some food elicits about the same response as in the fasting individual.

Nerve tension should be eliminated if possible. It is well known that excitement, anxiety and irritability increase the blood sugar level.

Smoking should be avoided or restricted after arising until the test is completed. Tobacco has been accredited with producing a rise of blood sugar, though whether this is always true or not remains to be determined, smoking before breakfast often induces nausea and vertigo, and consequently might interfere with the absorption of the glucose, the use of tobacco in many subjects is followed by nervousness and restlessness in others it has a soothing effect consequently on this score distinctive adjustments are in order.

Physical effort preceding and during a glucose tolerance test should be reduced to a minimum moderate exertion causes a rise in blood sugar, prolonged exercise depresses it.

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Menstruation lowers glucose tolerance, tests should not be carried out at the time of the menstrual period, nor a few days preceding or subsequent to it.

Complete starvation or carbohydrate starvation impairs the utilization of glucose Sweeney² formulated this fact more precisely when he established the fact that the diet for a forty-eight hour period will have a profound effect upon a sugar tolerance test in normal individuals. He showed that if an average (rather high carbohydrate) diet is taken for forty-eight hours, an increased glucose tolerance results, a high protein diet causes a moderate diminution in the test and a high fat diet or starvation, a marked diminution Conn³ has verified Sweeney's findings and in a very convincing presentation states. "Unless the influence of previous carbohydrate restriction is removed by an adequate preparatory diet (three to five days of a high carbohydrate diet), the glucose tolerance test is not reliable as an indicator of the individual's ability to utilize carbohydrate"

Another angle of the dietetic influence upon the glucose tolerance test is that when a diminished carbohydrate tolerance exists a preceding diet low in starches may shield the defect and yield a normal sugar tolerance test.⁴ Overweight calls for the consumption of larger amounts of glucose to keep the body warm and to move the extra pounds about. The insulin supply may prove inadequate to meet these increased demands, the pancreas becomes exhausted, less rather than more efficient, and diabetes ensues. There are many obese subjects who do not develop diabetes. On the other hand they should always be regarded with suspicion. When a glucose tolerance test is carried out in such cases, the preceding diet should be high in carbohydrate since in these, as in all latent diabetics, a low carbohydrate diet carried out for some days will often yield a normal sugar tolerance curve, which is misleading in prediabetics.

Dose of Glucose.—Glucose may be administered orally or intravenously. There is no doubt that the latter is more accurate since it avoids the irregularities of absorption that are a source of error in glucose tolerance tests. However, in routine clinical practice, the ingestion of glucose is decidedly more suitable and a revision of the test by intravenous administration may be considered for the few cases that show a persistently low blood sugar after the taking of glucose by mouth.

The test substance, almost always, is glucose (dextrose). Up to a few years ago it could be obtained only in the form of a messy syrup, or as dirty, large chunks that were weighed and dissolved with dif-

ficuity It is now available as a clean, white, dry granular preparation that is readily soluble in water One hundred grams can be taken up by 250 cc. of water, with the aid of heat if necessary This is best made ready the evening before the test and chilled in the refrigerator overnight The dissolved glucose should be flavored with lemon juice. Only one patient out of about a thousand vomited the ice cold glucose, and for him a second test, when coffee was substituted for the lemon flavoring, proved successful Other materials than glucose have been advocated and employed as test substances Here again it may be stated that because of the many hundreds of recorded tests in the literature, we are building upon a firmer background for the appraisal of our results in using glucose (dextrose), than when comparatively untried materials are selected

The amount of glucose most often given is 100 gm It has been reported that 75, 50 or even 25 gm. yield results that cannot be distinguished from those arrived at with 100 gm. There has been another school of thought on this matter—that the quantity of glucose be adjusted according to the weight of the patient, much as the action of drugs is measured per kilogram of animal The regulation of the dose of glucose to body weight entails a great deal of pointless detail Heavy persons contain no more muscular and glandular tissues than thin individuals but have only more fat which has no influence on the metabolism of glucose as far as the glucose tolerance test is concerned Furthermore, as has been mentioned, the results will be about the same whether 75 or 125 gm. of glucose are dispensed. Finally, a reiteration of what has been stressed several times previously, most of the data concerning sugar tolerance have been recorded after a test load of 100 gm. of glucose and we should take advantage of these as a basis for supplemental conclusions In one glucose tolerance procedure, the Exton Rose test,⁵ the glucose is given in two doses of 50 gm each, one-half hour apart This method, at first widely acclaimed, is no longer receiving enthusiastic endorsement We have never used or advocated it because we believe it is deficient in that it measures only the height of the blood sugar curve and not its duration A more detailed consideration of this problem will be taken up in a subsequent section on the standards for judging glucose tolerance test.

Choice of Blood Sugar Method—There are two types of blood sugar determinations in general use. One estimates the fermentable sugar, presumably glucose; the other includes certain other reducing substances The results of the first methods are often designated as "true glucose," while in the latter they are described as blood sugar,

implying that the nonglucose reducing materials are included in the figures for sugar. The blood sugar method of choice is usually the Folin-Wu procedure which includes the nonglucose, nonfermentable reducing materials as sugar. The difference between the Folin-Wu results and the values obtained for true blood sugar yields the figure for nonglucose reducing substances.

It has been the universal belief that the nonglucose reducing substances amount to 10 to 30 mg per 100 cc of blood. This inaccuracy in blood sugar determinations has been regarded as "slight" and also as "fairly constant."⁶ A check on this matter showed that in 200 consecutive blood sugar determinations (Table 1), 62 per cent were within the 30 mg limit but that 38 per cent were considerably above

TABLE 1

NONGLUCOSE REDUCING SUBSTANCES IN 200 CONSECUTIVE BLOOD SUGAR DETERMINATIONS IN NORMALS AND IN DIABETICS, IN THE FASTING STATE AND AFTER EATING

Nonglucose Reducing Substances Venous Blood, Mg per 100 Cc	Number of Cases	Per Cent	
0-10	40	20	62% within accepted normal limits
11-20	47	23 5	
21-30	37	18 5	
31-40	41	20 5	
41-50	15	7 5	38% above accepted normal limits
51-60	13	6 5	
61-70	3	1 5	
71-80	4	2 0	
TOTALS	200	100 0	

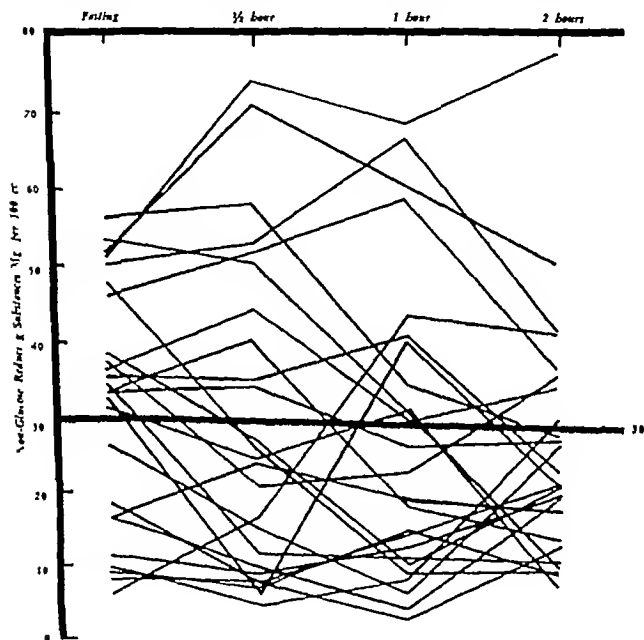
In 38 per cent of the determinations the amount of nonglucose reducing substances exceeded the accepted upper normal limit of 30 mg per 100 cc
(Mosenthal, H O and Barry, Eileen *Am J Digest Dis*, 13 160, 1946)

it. Since the nonglucose reducing substances have no bearing on the glucose or carbohydrate metabolism, a considerable error may be introduced in this way.

The nonglucose reducing substances vary a good deal from case to case and are often far from constant in the same individual (see Fig 43). Table 2 clearly illustrates how great a misjudgment may be made on glucose tolerance tests if the Folin-Wu method is employed instead of one for true blood sugar.

Arterial versus Venous Blood Sugar.—The sugar content of the capillary blood obtained from the finger tip has been shown to be identical to that found in the blood derived directly from the arteries.⁷ The arterial blood sugar in the fasting state is practically the same as

that found in the venous blood sugar. However, in the course of glucose tolerance tests there is a wide divergence between the arterial and venous blood sugar value. The arterio-venous difference after the administration of glucose was found to rise as high as 102 mg. and the



The marked fluctuations, without any definite pattern, are evident. Many determinations are above the accepted upper limit of 30 mg per 100 cc.

Fig 43—Non-glucose reducing substances in twenty five sugar tolerance tests. After 100 gm. of glucose (Mosenenthal H O and Barry, Eileen; Am J Digest. Dis., 13 160 1910)

average difference in twenty glucose tolerance tests was 80 mg. one-half hour after the ingestion of glucose, 42 mg one hour after, and 10 mg two hours after (Fig. 44)

It becomes evident that in glucose tolerance tests the arterio-venous blood sugar values are far apart and should be recorded dif

ferent interpretations, yet they are judged by the same standards in many laboratories. In England the capillary blood sugar is usually determined, while in this country the venous blood sugar is more frequently used.

The arterial blood circulates through the glomeruli and the blood sugar level within it is responsible for the degree of glucose filtration which occurs in the kidney. Therefore, for judging the renal threshold to glucose, arterial blood sugars are of crucial importance as compared to the venous blood sugars. Since there is such a marked arterio-venous blood sugar difference in the course of glucose toler-

TABLE 2
HIGH VALUES FOR NONGLUCOSE REDUCING SUBSTANCES IN A SUGAR TOLERANCE TEST

Timing	Venous Blood Sugar, Mg per 100 Cc. True Blood Sugar	Venous Blood Sugar, Mg per 100 Cc. Folin-Wu Method	Nonglucose Reducing Substances, Mg per 100 Cc.
Fasting	87	138	51
100 gm glucose by mouth			
One-half hour	102	176	74
One hour	109	178	69
Two hours	90	168	78

According to the true venous blood sugar this is a normal curve, while the Folin-Wu method indicates a diminished sugar tolerance. This is an example of the hazard of an erroneous interpretation of blood sugars when the analyses include nonfermentable substances, whereas the correct diagnosis is revealed by true blood sugar determinations.

Male (S B G), aged forty-four. Glycosuria found on life insurance examination seven or eight years ago, no glycosuria since that time.
(Mosenthal, H O and Barry, Eileen. *Am. J. Digest Dis.*, 13:160, 1946.)

ance tests (Fig 44) it becomes evident that the usual conception of the renal threshold to glucose is a faulty one. This has been summarized by Lawrence, who stated that in America the renal threshold to glucose is regarded as being at a level of about 170 mg, while in England it is put at a higher level as judged by the arterial standards. For the determination of the renal threshold to glucose, that is, the occurrence of renal glycosuria, it is perfectly evident that the arterial blood sugar should be resorted to. Our present conception of this subject, as determined by venous blood, lacks satisfactory accuracy (Table 3).

For the determination of the glucose tolerance, the venous blood sugar, representing as it does, the utilization of sugar that has gone on within the tissues between the arteries and the veins, is more informative than the arterial blood. The venous blood measures the metab-

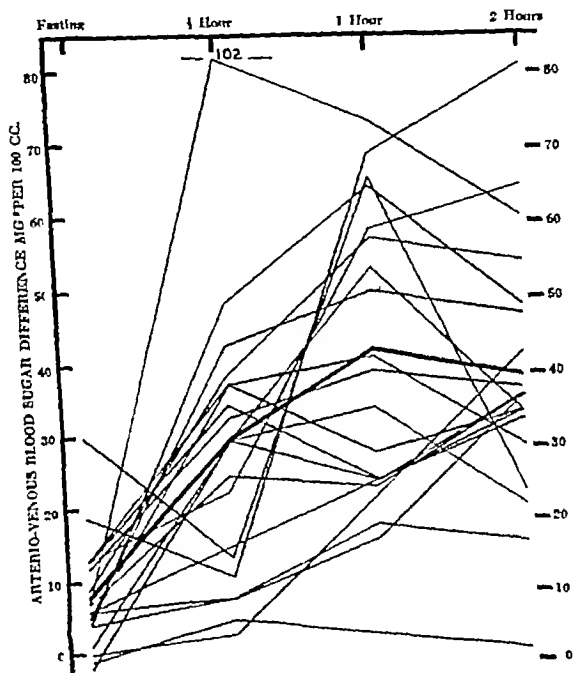


Fig. 44—Arterio-venous blood sugar difference after 100 gm. glucose. The marked rise of arterio-venous blood sugar difference after the taking of glucose is evident. The average difference (heavy line) is 8 mg. per 100 cc. fasting and 40 mg. two hours after glucose ingestion.

olism in certain directions which the arterial blood does not. In judging of the adequacy of carbohydrate metabolism by the glucose tolerance test the venous blood sugars appear to be distinctly more desirable. Frequently the venous blood sugar curve indicates a normal

TABLE 3

CASE ILLUSTRATING THE ADVISABILITY OF RELYING ON ARTERIAL BLOOD SUGAR FOR DETERMINING THE RENAL THRESHOLD TO GLUCOSE

Time	True Blood Sugar, Mg per 100 Cc		Urine	
	Arterial	Venous	Volume, Cc	Glucose, %
Fasting	77	81	55	0
100 gm glucose by mouth				
One-half hour	240	192	20	0
One hour	267	186	55	2 0
Two hours	213	162	105	2 5

The fasting blood sugar is normal. The height of the blood sugar curve hardly exceeds the normal in the venous blood sugar, whereas it is marked in the arterial blood. At the end of two hours both the venous and arterial blood sugar are distinctly above the normal. This curve, as far as glucose tolerance is concerned, is scarcely high but it is prolonged so that it would come in the category of impaired glucose tolerance.

The interesting point develops that while the venous blood sugar is dropping from the half-hour to the one-hour period, the arterial blood sugar is rising during the same interval. This would account for the appearance of glucose in the urine as judged by the arterial blood sugar levels but not by the venous. The significance of the arterial blood sugar level and the unimportance of the venous blood sugar level in producing glycosuria is very evident in this glucose tolerance curve.

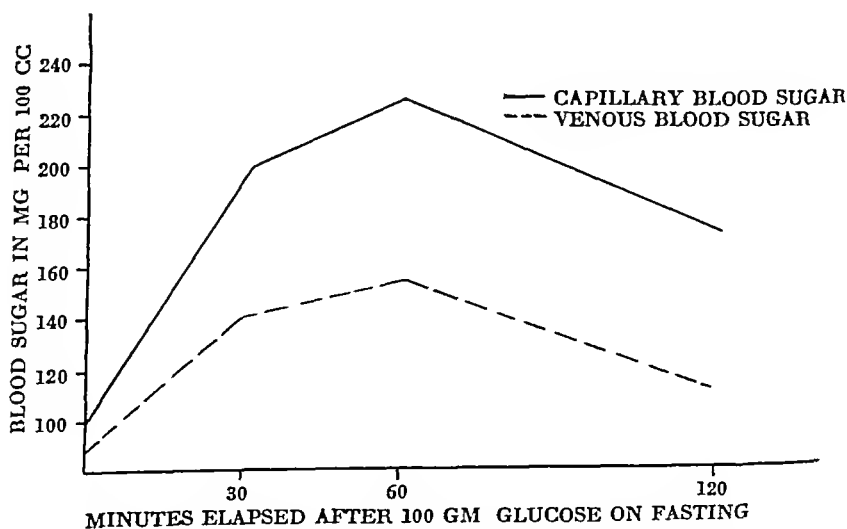


Fig 45—S S M, aged 47. Normal sugar tolerance shown by venous blood, impaired sugar tolerance by capillary blood. This man is probably not a diabetic though he was rejected by an insurance company because of capillary blood sugar curve.

glucose tolerance while the capillary does not (Fig. 45) For the reasons just given it is believed that the venous blood sugar yields a more reliable result.

Number of Blood Sugar Determinations.—A fasting blood sugar is always required. For a complete glucose tolerance test, blood sugar determinations, at least at the half-hour, one hour and two-hour intervals are desirable. Urine specimens for the determination of the presence of sugar should be obtained at the same time as the blood samples

STANDARDS FOR JUDGING GLUCOSE TOLERANCE TESTS

Fasting Blood Sugar Level.—The normal value is 120 mg. per 100 cc. or less. If the fasting blood sugar is significantly above this figure it is not worth carrying out the glucose tolerance test. An elevated fasting blood sugar is acknowledged by every one to indicate a diminished glucose tolerance.

Height of the Blood Sugar Curve—In normals the maximal elevation of the blood sugar after the ingestion of glucose is usually found within half an hour, though sometimes it develops a little later. The blood sugar determinations a half hour and one hour after the taking of glucose serve to give the approximate height to which the blood sugar rises. These blood sugar determinations, coupled with the results of the urine analyses, give an indication of the renal threshold to glucose. The normal height of the blood sugar curve varies a great deal. In young individuals it should not exceed 160 mg. per 100 cc. whereas in the elderly it often reaches 190 mg. It has been established for a long time and generally accepted, that the height of the blood sugar curve with a drop to a normal level at the end of two hours is not significant of a diminished glucose tolerance, that is, those curves which are designated as high curves unless they are also prolonged are not diagnostic of an impaired carbohydrate metabolism.

Duration of the Blood Sugar Curve—In normal individuals the blood sugar drops to a level of 120 mg. two hours after the taking of glucose. This is true in young subjects. In older persons with no impairment of glucose tolerance the two hour blood level may be considerably higher than this—up to 140 and even 150 mg. per 100 cc.

What Constitutes a Diabetic Blood Sugar Curve?—Every case of diabetes exhibits a high, prolonged blood sugar curve but not every instance of a high, prolonged blood sugar curve is one of diabetes. In other words, the carbohydrate metabolism may be impaired by more than one cause. We may roughly designate these as diabetic and

nondiabetic The differentiation between these two is exceedingly difficult and, more often than not, impossible It was mentioned previously that the two-dose tolerance test in our estimation was not satisfactory An explanation for this opinion can now be given The two-dose test measures only the height of the curve and it is well-known that a high curve, in the absence of prolongation of the curve, is not indicative of diabetes Any test which takes into consideration only the length of the curve, or the height of the curve, is not as free from diagnostic error as one that includes both the height and the duration of the curve.

Evaluation of the Patient's History.—In doubtful instances the history of the case is of distinct value in affirming or negating the diagnosis of diabetes The family history furnishing information concerning possible heredity is acknowledged to be of great value in determining whether or not the patient may be subject to diabetes

The history of glycosuria is extremely important. There are many instances in which sugar was found on one occasion and then, although the patient was free from sugar for a considerable number of years, he was still regarded as a diabetic This stretches a little too far the smug precept that the occurrence of sugar at any time is a final sign of diabetes The patient in Table 1 furnishes an example of this

The glucose tolerance curve with advancing years becomes distinctly higher and more prolonged, a curve which would be pathological for a person under 30, might be normal for an individual of sixty and over⁸ This has been shown time and again and while impairment of the glucose tolerance in the young should be taken very seriously, in the elderly an allowance, especially on the basis of the past history, should be made

According to the findings of Dr Bolduan and myself, married women over 45 are more prone to become subject to diabetes than are men or unmarried women This may be due to pregnancies, the presence of gallstones, or some other cause, but the fact remains that the married woman is much more frequently subject to diabetes than unmarried women, or men, whether married or not The past history of occurrence of epigastric pain should point to the possible existence of attacks not only of cholelithiasis, but also of pancreatitis Each of these would favor the diagnosis of diabetes In every instance of diminished glucose tolerance the suspicion of hyperthyroidism or hyperpituitarism should be entertained There are a good many patients in whom the tendency to diabetes disappears after subtotal thyroidectomy or after hyperpituitarism has subsided.

Case Judged According to History, Physical Examination and Glucose Tolerance

C. W. F., male, aged 65

Problem Significance of glycosuria found in March, 1946

History There has been no sugar demonstrated in the urine before or since March, 1946 Sugar tolerance test, carried out by an outside laboratory a few weeks ago, showed

Fasting blood sugar	129 mg per 100 cc.
One hour blood sugar	283 " " " "
Two hour blood sugar	289 " " " "

On a diet containing moderate quantities of starch, also some sweets such as vanilla ice cream and a vanilla cookie, the urine showed as follows

Time	Volume, Cc.	Specific Gravity	Sugar, %
8:00-10:00	100	1014	0
10:00-12:00	225	06	0
12:00-2:00	300	04	0
2:00-4:00	200	08	0
4:00-7:00	275	06	0
7:00-10:00	400	02	0
Total day	1500		
Total night	750	04	0
TOTAL	2250		

From these tests it may be gathered that the urine was negative for sugar throughout the twenty four hours in carefully analyzed specimens. The diet was rather high in starch and contained some sugar

There is no family history of diabetes.

There have been no episodes indicative of gallstone or pancreatitis.

Weight is constant at present and there have been no notable fluctuations of weight during the past decade.

Physical examination There was no anemia. Weight for height and age, blood pressure and eyegrounds were all normal Urine analysis and Wassermann reaction were negative.

Blood chemistry (taken after breakfast)

Sugar	108 mg per 100 cc.
Cholesterol	211 " " " "

The glucose tolerance test was as shown in Table 4.

The fasting blood sugar is within normal limits. The blood sugar rises with great rapidity after the taking of glucose to a very high level, and at the end of two hours is markedly above the accepted normal of 120 mg. Therefore this may be considered a high, prolonged glucose tolerance curve characteristic of an impaired glucose metab-

olism These figures are in exact conformity with those previously obtained.

It is well known that every case of diabetes has a high, prolonged blood glucose curve but not every high, prolonged glucose curve is one of diabetes In the clinical sense I do not believe Mr. C W F has diabetes There are several points to be taken into consideration on this score The patient is 65 years of age, at which period of life a high, prolonged curve often exists though diabetes is not present⁸ The history of finding sugar on only one occasion and not on others (and not in the twenty-four hour specimens obtained in fractionated samples) all point to the fact that in the clinical sense diabetes does not exist Sugar evidently appears in the urine only on rare occasions

TABLE 4

Time	True Blood Sugar, Mg per 100 Cc Venous	Urine	
		Volume, Cc	Glucose, %
Fasting	114	75	0
100 gm glucose by mouth			
One-half hour	218	25	0 1
One hour	268	15	1 5
Two hours	237	125	1 0

presumably when considerable amounts of sugar are indulged in It should be an easy matter to restrict the diet so that only moderate amounts of sugar or sugar-containing foods are used

Conclusion Impaired glucose tolerance in a man of 65 which has never become clinically manifest as diabetes and does not promise to do so in the future None of the stigmata (heredity, albuminuria, eye changes, cholelithiasis, pancreatitis, obesity) often found in mild or latent diabetes, are present here.

Diabetes does not exist in the clinical sense

Checking the urine and blood sugar at intervals would be an advisable precaution

SUMMARY

The technic of the glucose tolerance test and the advantage of using true venous blood sugar for the glucose tolerance test have been pointed out. Great care should be taken to see that the patient is in the best possible condition for a factual result A careful history and physical examination to determine whether there are any pre-

disposing factors towards rendering the glucose tolerance test abnormal should carry weight in judging the significance of a glucose tolerance test. Finally, it should be borne in mind that while every case of diabetes exhibits a high, prolonged blood sugar curve, not every case presenting a high prolonged blood sugar curve is one of diabetes.

The following may be a case in point

Dr A., now 72 years old, more than thirty years ago showed traces of sugar in his urine. A glucose tolerance test carried out in 1923 showed a high, prolonged curve as given in Table 5. The glucose tolerance test was repeated in 1929 and in 1937 and all of them yielded similar results. From the clinical point of view, for the past eighteen years this man has been taking a full diet including sugar

TABLE 5

A HIGH PROLONGED GLUCOSE TOLERANCE CURVE IN A PATIENT WHO IN MORE THAN TWENTY YEARS DID NOT DEVELOP DIABETES

Time	Blood Sugar Mg per 100 Cc.	Urine		Remarks
		Volume Cc.	Glucose, %	
9-08	117	124	0	Fasting
9 14—100 gm glucose by mouth				
9 37	242	40	0	
9 58	283	15	1 1	
10 10	200	14	1 4	
11 17	250	58	2 0	

Several other glucose tolerance tests were carried out and they all duplicated the results shown above. This is an instance in which a high, prolonged glucose curve was not diagnostic of diabetes.

and desserts without ever exhibiting glycosuria and his blood sugars, taken after meals were distinctly on the low side, the last three being 74, 91 and 84 mg per 100 cc. In fact at times when the postprandial blood sugar was as low as 60 mg., it was feared that there might be an essential hypoglycemia. This individual, like many others, has suffered because of unnecessary treatment for diabetes inflicted on him for some years and also by not receiving life insurance at the most favorable rates.

For the estimation of the renal threshold to glucose or the "kidney leak point," arterial blood sugars are necessary. The venous blood

sugar levels widely employed for this purpose are very misleading and new criteria are urgently needed. A low renal threshold to glucose, that is, a renal glycosuria, is a harmless anomaly and should be sharply distinguished from diabetes mellitus. It is true that the two conditions may at times occur simultaneously, but this does not absolve the physician from the responsibility of according the uncomplicated cases individual treatment and not an all-covering attention adopted to glycosuria regardless of its cause.

For the estimation of the soundness of carbohydrate metabolism, venous blood is preferable. After glucose ingestion the venous blood is much lower than the arterial (or capillary) blood and this difference is one of the measures of glucose utilization.

Only methods yielding "true blood sugar" values should be used in carrying out glucose tolerance tests, since an inclusion of the so-called nonglucose reducing substances in the figures for blood sugar may lead to serious errors.

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THE DIAGNOSIS OF THE LESS COMMON MELITURIAS

Including Pentosuria and Fructosuria

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DESPITE the fact that much has been written and said regarding the importance of proper differential diagnosis of the meliturias, all too often patients with benign conditions are thought incorrectly to have diabetes mellitus and treated for such over long periods of time. It is essential that the physician have in mind a clear and concise outline of the steps to be taken in differential diagnosis. Consequently, in this paper we shall present diagnostic rules which facilitate the identification of rarer sugars in the urine and review our experience with patients who have come under our observation. This experience includes nine patients with pentosuria and four with fructosuria which have been noted among approximately 29,000 patients with melituria. It is almost certain that other patients with benign melituria, apart from glycosuria, remain unrecognized. In the following presentation, renal glycosuria and other forms of nondiabetic *glycosuria* will not be discussed in detail.

TYPES OF MELITURIA

The types of melituria may be classified as follows:

1. Diabetes mellitus.
2. Potential diabetes.
3. Renal glycosuria.
4. "Unclassified" glycosuria.
5. Melituria other than glycosuria
 - (a) Lactosuria
 - (b) Galactosuria
 - (c) Maltosuria
 - (d) Mannohexptulosuria
 - (e) Pentosuria
 - (f) Fructosuria
 - (g) Sucrosuria

It is our practice to make the diagnosis of *diabetes* if, in an individual with glycosuria, the fasting blood sugar is 130 mg. or more per

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100 cc, or following a meal or following glucose given under standard and controlled conditions the venous blood sugar is 170 mg or more per 100 cc. Diagnostic standards must of necessity be set arbitrarily and are therefore subject to criticism. Particularly is this so in the case of postprandial capillary blood sugar values. We prefer to use venous blood for diagnosis but in cases, in which capillary samples are taken, we regard as abnormal a value of 200 mg or more per 100 cc following food or glucose.⁷

The diagnosis of *potential diabetes* is useful in those individuals with glycosuria closely related to diet, who easily become sugar-free with slight restrictions and in whom the blood sugar is below 130 mg. fasting and never quite reaches 170 mg per 100 cc. following a meal.

Renal glycosuria is a condition in which the sugar which appears in the urine reflects a renal threshold for glucose which is lower than the average normal. It is our custom to make the diagnostic standards more strict by reserving the diagnosis for those persons in whom the renal threshold is so low that sugar appears in the urine constantly even in the fasting state. Except possibly for some tendency to lassitude and malaise in those persons who constantly excrete large amounts of sugar, the condition is asymptomatic and is benign with no tendency to progression to diabetes mellitus.

Under the heading of "*unclassified*" *glycosuria* are included the conditions of those individuals in whom glycosuria, usually slight, variable and temporary, occurs as a manifestation of other abnormalities. These include hyperthyroidism, hyperpituitarism and conditions in which the suprarenal glands are affected, brain tumor, cerebral hemorrhage and skull injuries, alimentary glycosuria and "hunger glycosuria", infections and toxemias, chronic and degenerative conditions such as chronic nephritis and nephrosis, chronic disease of the liver, hypertension and malignant disease, toxic effect of various chemicals, including the effect of anesthesia and asphyxia.

Certain of the *meliturias other than glycosuria* will be mentioned only briefly. *Lactosuria* is a physiological event during lactation and the last days of pregnancy. However, the sugar which frequently appears during the greater part of pregnancy is practically always glucose and is a reflection of the temporary lowering of the renal threshold for sugar (*renal glycosuria of pregnancy*). Lactose is not easy to identify in the presence of glucose. Like glucose, it reduces copper solutions and is dextrorotatory, although it yields a characteristic osazone with phenylhydrazine and is not fermented by pure yeast, the osazone is difficult to obtain from the urine and ordinary

yeast cannot be depended upon for the fermentation test. Qualitative tests for lactose are the mucic acid test and Rubner's test. Fortunately, the condition in which lactosuria characteristically occurs, namely lactation, is usually evident to the physician and the presumptive diagnosis is obvious. In the article by Watkins¹ are given the results of an extensive study of lactose metabolism in women.

Spontaneous *galactosuria* is a rare condition of little importance clinically. A few cases have been reported, chiefly in pediatric literature. As an example may be cited the patient of Bruck and Rapoport,² a 7 week old male infant, in whom galactosemia was associated with galactosuria, albuminuria, anemia, failure to gain and develop normally, vomiting, lethargy, bilateral cataracts, hepatomegaly, absence of tendon reflexes and increase in the spinal fluid protein. All abnormalities, including the cataracts, disappeared gradually after milk was omitted from the diet. Following studies in a somewhat similar case, Norman and Fashena³ regard the condition as an inborn error of metabolism and suggest that the essential defect probably lies in the specific enzyme system concerned with the conversion of galactose to glycogen.

Maltosuria has been demonstrated only rarely and has not been shown to be of clinical significance.

Mannoheptulosuria was found by Blatherwick, Larson and Sawyer⁴ to occur in ten normal persons following the ingestion of 136 to 214 gm. of avocado. The amounts of sugar in the urine were small, varying from 0.06 to 0.32 per cent. Mannoheptulose is a nonfermentable sugar which reduces Benedict's solution without heating as do pentose and fructose.

Sucrosuria has been reported only rarely and has but little clinical significance. Like pentosuria and fructosuria, it is no doubt due to a metabolic defect or error although the nature of such is not clear. Elmer, Krasowska and Ptaszek⁵ recognize two forms, an exogenous in which sucrose appears in the urine only after the ingestion of cane sugar and an endogenous type in which sucrosuria occurs independent of the intake of cane sugar. They regard the exogenous or alimentary form to be due probably to impaired sucrolytic activity in the digestive tract. The endogenous type was believed by them to be associated with unidentified alterations in pancreatic, and perhaps hepatic function. A characteristic finding in the cases of Elmer and his associates was an extremely high specific gravity of the urine up to 1.070. In Hoersch's⁶ case the specific gravity of the urine was very high, ranging from 1.100 to 1.145.

It was the high specific gravity of the urine which directed our attention to the possibility of sucrosuria in Case 19260, that of a woman born January 21, 1916, with discovery of melituria in January 1939. At an office visit on October 28, 1946 our colleague, Dr C C Bailey, noted that the specific gravity of the urine was 1.056 despite the fact that the Benedict's test was negative. Scrutiny of the patient's record disclosed that since August 9, 1945 the specific gravity of the urine had been recorded at eight of ten office visits as above 1.050 (of the two remaining, one was 1.045 and the other 1.021) although at numerous examinations in the five years prior to this, values in the customary range had been found. Because of the report of Elmer and his co-workers, the urine obtained at a recent visit was hydrolyzed with hydrochloric acid and then tested for sugar by Benedict's method. Whereas before hydrolysis less than 0.1 per cent sugar was found, after hydrolysis a value of 2.9 per cent was obtained and the Seliwanoff test was positive. Deception, always to be kept in mind in cases of apparent sucrosuria, has not been proved. However, examination of specimens subsequently has not revealed a high specific gravity or other results consistent with sucrosuria. Further studies are in progress to determine the validity of the case.

PENTOSURIA

Chronic essential pentosuria is a rare, benign condition characterized by the constant presence in the urine of small quantities of pentose, usually xylulose. The condition is asymptomatic, harmless and has no relation to diabetes mellitus. It is to be regarded also as an "inborn error of metabolism", some⁶ have regarded glycuronic acid as the mother substance of the pentose. All reported cases have been in Jews and predominantly in males. The studies of Lasker^{7,8} and others leave no doubt but that pentosuria is inherited, apparently as a mendelian recessive trait. It seems likely that most of the families of pentosurics, at least those now living in the New York area and studied by Lasker, came from foci of relatively limited extent in Eastern Europe, largely in Poland and Germany.

Pentose, a keto-sugar, reduces Benedict's solution at room temperature over a period of a few hours or at 50° to 60° C. in ten minutes. At boiling temperature the reduction by pentose begins within one minute of the time the tube is placed in the water bath. Pentose is not optically active nor is it fermented by yeast. It gives a positive *Bial test*. The reagent used in this test has the following composition

Orcinol	1.5 gm.
Fuming hydrochloric acid	500 gm.
Ferric chloride (10 per cent)	20 to 30 drops

The test is performed as follows To 5 cc. of the reagent in a test tube add 2 to 3 cc. of urine and heat the mixture gently until the first bubbles rise to the surface Immediately or upon cooling in the presence of pentose, the solution becomes green and a flocculent green precipitate may form.

A characteristic osazone is formed with phenylhydrazine which has a melting point of 157° to 160° C

The patient described below illustrates the confusion which may arise in a case of pentosuria and the gratification of making the correct diagnosis

CASE I (Clinic No 18070) —A Jewish boy, born May 9, 1935, was first seen on July 17, 1939 when the parents brought him for observation from their home in a distant city Sugar had been found in the urine first in March 1937 at a routine examination Since melituria was found to be constant, a glucose tolerance test was carried out which was interpreted as indicating diabetes The child was placed on a restricted diet and treatment with unmodified insulin instituted in an amount of 16 units daily in three doses before meals Subsequently, because of insulin reactions the injections before lunch and supper were discontinued and the dose before breakfast reduced so that at the time the patient was first seen here, the amount was 3 units before breakfast Under treatment, the child had gained in weight and strength

At the first visit here a random specimen of urine contained 0.3 per cent sugar and a random capillary blood sugar was 0.16 per cent. It was noted that in boiling water the Benedict test showed beginning of reduction in 30 to 35 seconds and even at room temperature Benedict's solution was reduced in several hours The Bial test was positive and the Seliwanoff test negative No fermentation was observed with yeast. Physical examination and routine studies apart from melituria yielded essentially normal results Treatment with insulin was discontinued and an unrestricted diet provided Almost without exception, urine specimens obtained seven times daily continued to show sugar but always in uniformly small amounts (green tests with Benedict's solution) On July 24 1939 the patient was given 34 gm. of glucose by mouth (1 gm per pound of body weight) and the results shown on page 319 were obtained.

On the basis of these findings it was concluded that the diagnosis was not diabetes but rather chronic essential pentosuria Subsequently

TABLE 1
SUMMARY OF DATA ON CASES OF MELITURIA*
A PENTOSURIA

No	Case Number	Sex	Age at Discovery of Melituria	Duration of Known Melituria	Melituria in Relatives	Urinary Sugar		Urine Tests				Blood Sugar Highest Values, Per Cent		Glucose Tolerance Tests				
						High	Low	Fermentation with Yeast	Bial	Selwanoff	Osazone Melting Point	Fast-ing	After Food or Sugar	Glu-cose	Fast-ing	Hours after Glucose		
						Per Cent	Cent									1/2	1	2
1	1473	M	27 6	29 8	0	1 5	0 1	0	+	0	157-159	0 10	0 12	Gm	—	—	—	—
2	1484	F	9 9	29 7	0	0 6	0 2	—	+	0	159-160†	0 10	0 12	—	—	—	—	—
3	6629	F	18 2	19 0	+	0 6	Trace	0	+	0	—	0 10	0 17	75†	0 10	0 14	0 11	0 10
4	6760	M	12 3	26 7	+	0 8	0	0	+	0	160	0 09	0 11	—	—	—	—	—
5	7995	M	4 3	21 2	+	0 5	0	0	+	0	154	—	0 15	40	—	—	0 12	0 12
6	13676	M	31 8	11 8	+	0 8	0 1	0	+	0	—	0 08	0 09	100	0 09	0 17	0 13	0 09
7	16923	M	38 0	8 6	+	1 3	0	—	+	0	150†	0 08	0 17	34	0 11	0 12	0 11	0 11
8	18070	M	1 8	9 8	+	0 6	0	0	+	0	—	0 10	0 12	—	—	—	—	—
9	18217	M	9 3	8 1	0	0 4	0 4	0	+	0	—	—	0 08	—	—	—	—	—

B FRUCTOSURIA

1	7157	M	3 7	21 3	+	1 4	0 3	—	0	+	—	—	0 14	—	—	—	—	—
2	13228	M	17 8	14 7	+	1 8	0	+	0	+	152 5	0 07	0 15	100	0 07	0 12	0 12	0 10
3	15117	F	1 3	14 4	0	2 0	0	+	0	+	—	0 09	0 17	46	0 09	0 17	0 15	0 13
4	21113	F	18 3	5 1	+	2 7	—	—	0	+	—	0 09	0 11	—	—	—	—	—

* All patients are Jewish except Case 19260 with sucrosuria
† Data supplied by Mrs Margaret Lasker
‡ Cane sugar was used

Time	Urine			Capillary Blood Sugar Per Cent
	Volume, Cc.	Specific Gravity	Sugar Per Cent	
Fasting	20		0 3	0 11
1 hr after glucose	18	1020	0 4	0 12
1 hr after glucose	50	1008	0	0 11
2 hrs. after glucose	75	1006	0	0 11

the findings were confirmed by Mrs Margaret Lasker of New York who identified the pentose as *l* xylulose.

The patient was discharged with the statement that the melituria was harmless and that no treatment was indicated, much to the joy of the parents. He has continued well in the more than seven years since that time. A letter received from the father in 1946 stated that he "has been enjoying practically perfect health ever since his return from Boston and is developing mentally and physically in a most satisfactory manner. His school record is excellent and he is very active in sports, particularly swimming, at which he is very proficient."

As stated at the beginning of this paper, our experience includes nine patients with proved pentosuria. Their cases are summarized in Table 1. Not infrequently, the sequence of events in their histories has been about as follows: sugar in small amounts has been found in the urine at a routine examination and the diagnosis of diabetes made followed by institution of treatment with a restricted diet with or without insulin; then with some the nondiabetic nature of the disorder has become evident because of lack of hyperglycemia, and the diagnosis of renal glycosuria or other benign glycosuria made, and finally the correct diagnosis of pentosuria has been established following more careful study of the type of sugar excreted in the urine.

FRUCTOSURIA

Fructosuria (levulosuria) is like pentosuria a harmless condition due to a metabolic defect and is undoubtedly inherited. It is even rarer than pentosuria and in our own series only four cases have been recognized: two of them in a brother and sister. These four cases, all in young Jewish persons, are summarized in Table 1. In individuals with essential fructosuria, the rate of removal of fructose* from the blood stream is retarded with the result that following the ingestion of this sugar, a blood fructose level well above the renal threshold

for fructose is temporarily maintained and fructosuria results. Presumably the removal of fructose from the blood is normally cared for in large part by the liver, this function is impaired in the patient with fructosuria despite the fact that there may be no other evidence of hepatic dysfunction. In one normal subject studied by us⁹ the renal threshold for fructose was found to be about 11 mg per 100 cc. of blood fructose.

Fructose, as well as glucose, is said to occur in the urine in patients with severe diabetes. Our experience affords very little data on this point, although in Case 12377, in which the patient was a young Jewish woman with mild diabetes, aged 13 4 years at the time of discovery of melituria in April 1931, fructosuria and glycosuria were associated. Studies in this case have been reported.⁹ It may be significant that the cause of death of this patient who died on July 13, 1938 was reported as cirrhosis of the liver.

Fructose is levorotatory, is fermented by yeast and, like pentose, reduces copper solutions at room temperature after several hours or within ten minutes at 50° to 60° C. With phenylhydrazine, fructose yields the same osazone as glucose so that for differentiation it is necessary to use methylphenylhydrazine with which fructose gives a characteristic osazone with a melting point of 153° C. If the test is carefully performed and certain precautions taken, fructose can be differentiated from other sugars by the *Selwanoff reaction* which is performed as follows:

Place in a test tube equal quantities (2 or 3 cc. each) of urine and 25 per cent hydrochloric acid. Bring to boiling over a free flame. Add a few crystals of resorcinol and boil actively for 10 seconds. If fructose is present, almost immediately the solution becomes red and a dense reddish-brown precipitate forms. This precipitate is soluble in alcohol.

The following case report again illustrates the confusion which may arise in the diagnosis of a case of melituria and the importance of carrying out careful studies:

CASE II (Clinic No. 15117) —A Jewish girl was first seen on July 24, 1936 at the age of 5 years. Sugar had been found in the urine first in July 1932 or thereabouts and at that time was thought to be pentose. Symptoms had been ill-defined but the question of diabetes mellitus had been raised because of loss of weight and strength, irritability, and questionable polyuria and polydipsia. Physical examination on July 24, 1936 was essentially normal. The child was 48 inches tall, with shoes and weighed 46½ pounds with clothing. A random speci-

men of urine contained 35 per cent sugar and a random capillary blood sugar was 0.10 per cent. The Bial test was negative but the Selwanoff test was positive. A glucose tolerance test was normal.

Opportunity was not afforded for detailed studies until in June 1941 when the child, now 10 years old, was again seen. Physical examination was normal, the height was 57 $\frac{5}{8}$ inches without shoes and the weight was 98 $\frac{1}{2}$ pounds with clothing. A random specimen of urine contained 1.4 per cent sugar and a random capillary blood sugar was 127 mg. per 100 cc. Frequent examination of the urine during a hospital stay showed sugar in small amounts in most specimens although a few were sugar-free and one gave as much as a yellow test with Benedict's solution. One glucose tolerance test carried out with 100 gm of glucoso gave capillary blood sugar values suggestive of diabetes, the fasting value was reported as 140 mg, the peak value at one hour as 234 mg. and the two hour value as 164 mg. per 100 cc. However, the test was repeated six days later using venous blood with the following results:

Time	Urine		Venous Blood Sugar, Per Cent
	Volume, Cc.	Sugar Per Cent	
Fasting	—	—	0.07
40 min. after glucose	41	0.1	0.17
105 min. after glucose	90	0.2	0.08
120 min. after glucose	21	0	0.11
195 min. after glucose	21	0	0.10

The above findings were considered as probably normal despite the peak value of 0.17 per cent although some reservation was made as to finality of diagnosis in view of this and in view of the glucose tolerance test mentioned above which had been carried out six days before with capillary blood. However a fructose tolerance test carried out on June 30, 1941 left no doubt as to the presence of fructosuria. After an overnight fast, 40 gm of fructose were given by mouth and urine and blood samples collected at intervals afterward with the results given on following page.

Analyses showed that practically all, if not all, of the sugar which appeared in the urine during the test was fructose (Fructose was determined in blood and urine by Roe's method¹⁰).

Without dietary or other treatment this patient has continued well and word received in 1946 indicated that her physical condition was excellent.

Time	Urine Sugar, Gm	Capillary Blood Sugar (Total), Mg per 100 Cc	Venous Blood Sugar		
			Total Sugar, Mg per 100 Cc	Fructose, Mg per 100 Cc	Glucose by Difference Mg per 100 Cc.
Fasting	Trace	89	91	Trace	91
30 min after fructose	0 38	138	123	44	79
60 min after fructose	0 92	175	135	50	85
120 min. after fructose	1 52	121	112	27	85
180 min. after fructose	0 52	96	95	13	82

SUMMARY OF FINDINGS IN PATIENTS WITH PENTOSURIA AND FRUCTOSURIA

In Table 1 are summarized certain of the findings in our patients with pentosuria and fructosuria. The data are in some respects incomplete since it has not been possible to carry out detailed studies with most of the group. In all cases the patients are Jewish. All are living and are free of symptoms which might be attributed to melituria.

Pentosuria.—Of the nine patients with pentosuria, seven are males. The age at discovery of melituria varied from 18 to 38 0 years and the duration of known melituria (to December 1946) is from 8 1 to 29 8 years. Three of the patients have had known melituria for more than twenty-five years. In six of the nine patients there is a history of melituria in relatives. The amount of sugar in the urine has usually been relatively small although occasionally it has been as great as 15 per cent. Although certain specimens of urine examined routinely have been reported as free from sugar, it is possible that more careful studies in these instances would have disclosed tiny amounts. The sugar was uniformly not fermented by bakers' yeast. The Bial test was positive and the Selwanoff test negative in all cases. In five patients the characteristic pentosazone was formed with phenylhydrazine. With the exception of borderline figures in two cases, all blood sugar values were within normal limits.

Fructosuria.—Two of the patients with fructosuria are males and two females. The age at discovery of melituria varied from 13 to 18 3 years. The duration of melituria to December 1946 ranged from 5 1 to 21 3 years. A family history of melituria was obtained in three of the four patients. The amount of sugar in the urine was subject to considerable variation. Fermentation with yeast occurred in the two cases tested. The Bial test was uniformly negative and the

Seliwanoff test positive In the one case so studied, the characteristic fructosazone was formed with methylphenylhydrazine With the exception of borderline values in Case 15117, all blood sugar figures were normal

DIAGNOSTIC STEPS

Given a patient with melituria, the following steps constitute a logical sequence of action which should lead to the correct diagnosis

- 1 A careful examination of the patient's history, physical findings and hereditary background

2. Examination at the first visit of random specimens of urine and blood for sugar If the results are not conclusive, then—

- 3 Examination of the urine and blood for sugar at forty-five to sixty minutes after a meal liberal in carbohydrate If these values are not definitely abnormal, the patient may be asked to return one or more times for additional determinations of the urine and blood sugar after a meal In cases of doubt, then—

- 4 Carrying out of a formal glucose tolerance test. Such a test should not be imposed on individuals with known diabetes or on those in whom the diagnosis can be made by single determinations of the blood and urine sugar after a meal If carried out, the subject should have been on an unrestricted diet and not have taken insulin for at least three days and should not be suffering from an infection or fever Some have used the Exton Rose (one hour, two-dose) procedure, but we have found the standard glucose tolerance test more satisfactory, giving adults a single dose of 100 gm of glucose by mouth and taking venous blood samples before, and at 30, 60 and 120 minutes afterward. In children 1.9 gm per kilogram of body weight (or roughly 1 gm per pound) are given

- 5 In cases of persistent melituria, despite normal blood sugar values even during a tolerance test, identification of the type of sugar excreted is necessary The following procedures are helpful in such a study

- (a) Carrying out of the Benedict's test at 50° to 60° C. for ten minutes or at room temperature for a few hours Under such conditions keto-sugars as pentose, fructose and mannheptulose cause a reduction of copper solutions whereas other sugars do not, unless present in large amount In this connection use may be made also of the disodium-dinitro-salicylate reagent described by Exton¹² This reagent is reduced at different rates by different sugars so that by keeping the temperature of a bath constant and noting the presence

or absence of reduction after certain stated intervals of time, differentiation of the reducing sugar is possible

(b) Fermentation with bakers' yeast Glucose and fructose are always, galactose usually, lactose occasionally, pentose and mannose-heptulose never, fermented

(c) Qualitative tests more or less specific for certain sugars

Pentose	Bial (orcinol-hydrochloric acid) test.
Fructose.	Seliwanoff (resorcinol-hydrochloric acid) test.
Galactose	Tollen (phloroglucinol-hydrochloric acid) test.
Lactose and galactose	Mucic acid test.

(d) Polariscope The direction and degree of rotation of polarized light as determined with a polariscope may be used as an aid in the identification of the type of urinary sugar Thus, glucose is dextrorotatory and fructose is levorotatory whereas pentose is optically inactive. However, the procedure is not now commonly used in clinical laboratories.

(e) Fermentation reactions with specific bacteria and fungi.¹³ These are not in general use in clinical laboratories

(f) Phenylhydrazine test. Osazone crystals with phenylhydrazine or methylphenylhydrazine (the latter in the case of fructose) can be prepared which have a characteristic appearance microscopically As a final step in identification, the crystals may be purified and the melting point determined

SUMMARY

1. The importance of correct diagnosis in patients with melituria is pointed out and illustrative cases described with particular reference to pentosuria and fructosuria

2. An outline of steps to be followed in diagnosis is presented In cases of persistent normoglycemic melituria the following tests are especially helpful (a) reduction of copper solutions in a few to several hours at room temperature or within ten minutes at 50° to 60° C by keto-sugars as pentose and fructose, (b) lack of fermentation of pentose by bakers' yeast, (c) the Bial test which is positive for pentose and the Seliwanoff test which is positive for fructose, (d) preparation of characteristic osazones with phenylhydrazine (methylphenylhydrazine for fructose).

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EFFECTIVE INSULIN TIMING IN DIABETES MELLITUS

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INTEREST in modifications of insulin with variable time-activity has increased during the last several years. Many reports of their usefulness in routine treatment of diabetes mellitus and careful studies of their nature have been made. Knowledge regarding the results of treatment has accumulated in the experience of many clinicians using various improved preparations and certain conclusions regarding standard methods of using depot insulins have evolved from this experience.

Uncertainty regarding the best therapeutic methods arises chiefly from two sources. First, the number of preparations of insulin has grown to the point that only investigators familiar with the detailed characteristics of each of them can keep their indications clearly in mind. Second, each proponent of a new preparation emphasizes its presumed advantages out of proportion to its true position in the picture.

The facts of the matter are comparatively simple. An attempt to present them in simplified form is the purpose of this paper. Typical results of treatment with a typical preparation are presented, not with the intention of promoting the virtues of that particular preparation, but as a means of illustrating the fact that an insulin of that type is needed for improved therapy in diabetes mellitus, and that its manufacture can simplify a problem which has led to considerable confusion and misunderstanding.

In order of their appearance, four types of insulin have become available for routine treatment of diabetes. Each of them has a characteristic rate of action and hence occupies its own position in diabetic therapy. They are insulin, protamine zinc insulin, globin insulin with zinc and mixtures or modifications of protamine zinc insulin.

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UNMODIFIED INSULIN

In so far as is known, this represents the true hormone in slightly acid solution in an unmodified state. It is the original form of insulin. All modifications stem from it and do not alter its action except as they prolong, delay or extend the rate at which the hormone is released from the site of a subcutaneous injection.

In solution insulin is administered by subcutaneous injection, as a rule, although it is occasionally given by vein or into the muscle without affecting the rate or intensity of its action profoundly. It is virtually ineffective except when given parenterally. Because it is a simple solution of the pure hormone its rate of action is the most prompt and least prolonged of all insulins. These characteristics cannot be changed much by variations in parenteral route of administration or changes in dosage.

Action.—Different diabetic patients vary somewhat in response to administration of the hormone in solution, but not so much in the rate of its activity as in the size of the dosage required to produce a given response. Making due allowances for differences in "insulin-sensitivity" and therefore the amount of insulin required to accomplish a given result, diabetic patients are surprisingly uniform in the rate at which they react to insulin in solution. On the average the response to a single subcutaneous dose is demonstrable within an hour, reaches its peak in from three to six hours after injection, and is exhausted in about eight to twelve hours¹ (Table 1). All of these values are greater with larger doses and less with smaller ones, but in amounts within the therapeutic range are roughly as described for insulin in solution.

The value concerning which there might be the most debate is the duration of action. The rate at which the sugar level reverts to its former position, however, depends more on the severity of the diabetes than on the duration of action of the insulin dose. Obviously in mild diabetes the rate of return of hyperglycemia on waning of insulin action, and therefore the apparent duration of effect, will be much slower than in severe diabetes, and yet the duration of action may be the same. The span of activity seen in severe diabetes is therefore more nearly the true value, namely, from eight to twelve hours for a single dose. In the case of modifications of insulin the same qualifications regarding duration are also most pertinent. Failure to appreciate them is responsible for some of the uncertainty regarding different forms of insulin.

These rates of action are characteristic of both forms of insulin.

in solution, "regular" or solution of amorphous insulin, and "crystalline" or solution of zinc insulin crystals. The latter is very slightly less prompt and intense and more prolonged in effect than the former, because of its higher zinc content,² but the difference is insignificant as compared with the changes produced by other modifications of insulin. The only difference of importance is the fact that "regular" insulin occasionally leads to allergic reactions because of its inert protein content, whereas the crystalline form is much less likely to do so because of its freedom from foreign protein.

Use—Because of its characteristic time-activity, insulin in solution is most useful whenever prompt and intense effect is desirable and

TABLE 1

TIME-ACTIVITY OF SINGLE LARGE DOSES OF VARIOUS TYPES OF INSULIN IN DIABETES OF MODERATE SEVERITY (APPROXIMATE)*

Type of Insulin	Action Demonstrable	Peak Action	Intensity at Peak	Duration of Effect
Regular or Crystalline	1 hour	3-6 hours	Strong	8-12 hours
Globin with Zinc	2 hours	8-12 hours	Fairly strong	24 hours at most
21 Mixture	4 hours	12-16 hours	Moderate	1½ to 2 days
Protamine Zinc	4-8 hours	24-32 hours	Weak	3 days or more

* Summarized from timing studies of single doses reported previously: 1, 2, 3.

prolonged effect is of little or no importance. In diabetic practice this involves three main indications for its use.

1 It is the insulin of choice in emergencies where quick action is essential, namely, in acidosis, infection, trauma, surgery, anesthesia and other acute complications in which the sugar balance is disturbed violently. In such cases it must be given in decisive dosage promptly. Repeated doses are necessary but they should be spaced in such a way that the effect of the preceding dose is evident before the next dose is given and the subsequent dose should be given before the effect of the previous dose is exhausted. On this account diabetes complicated by acute illness requires rhythmic administration of insulin in solution every four to eight hours or so. Injections more

than twelve hours apart fail to maintain continuous overlapping insulin effect. They may be cumulative, similar to the sum of the individual doses, if given more often than every four hours or so.

2 Ordinary insulin is useful in supplementing depot insulin effects when necessary. This is particularly true when depot insulin therapy is inefficient and poorly fitted to the requirements of the patient. It will be shown later that a depot insulin need not be inefficient in the majority of patients with diabetes mellitus, but until an efficient preparation is used generally, supplementation of present depot preparations by insulin in solution will be distinctly advantageous in a large fraction of the insulin-treated diabetic population. This is particularly true of protamine zinc insulin, probably the most widely used of the depot insulins. Detailed methods of supplementation will be described in the section on therapeutic use of protamine zinc insulin.

3 A few patients find ordinary insulin more practical for routine use without any depot preparation, even though multiple daily injections are required. There are three classes of patients in which this is true. First, and most important, the occasional patient with a high insulin requirement of more than about 150 units daily finds the volume too large with depot insulins and prefers to take two or more injections daily of a concentrated insulin in solution. Concentrations of 500 units per cubic centimeter are available on demand for such patients, whereas the strongest depot insulin contains only 80 units per cubic centimeter. Second, some patients have tried and been unable to maintain uniform control with inefficient depot insulins and find that multiple daily injections of insulin in solution provide a smoother balance. Frequently this program involves the necessity of an injection during the night to avoid a wave of glycosuria before and after breakfast. Improvements in depot insulin therapy have enabled many of these patients to obtain smoother control with only one morning injection daily. Third, many patients continue to use unmodified insulin because they have never tried to become regulated on depot insulin therapy.

PROTAMINE ZINC INSULIN

In North America this is the most popular and oldest of the depot insulins. As devised by Hagedorn³ and introduced by Joslin and his associates⁴ in 1936, it suspends insulin in the form of a relatively insoluble compound with a protamine in a buffered vehicle. When the uniformly mixed suspension is injected subcutaneously a depot is

formed which releases insulin slowly and somewhat uncertainly, thus prolonging and weakening the action of each single dose to the extent that injections only once daily are most suitable and heavy overlapping of effect is apparent from day to day. Zinc, originally incorporated chiefly for the purpose of increasing the stability of the preparation,⁵ delayed and prolonged the rate of insulin release beyond that planned by Hagedorn, probably by inhibiting an enzymatic process responsible for the separation of insulin from its precipitating protamine in tissue fluids.⁶

Action—Careful studies of the time-activity of protamine zinc insulin in human diabetes of moderate severity¹ reveal that the characteristic effect of single large subcutaneous doses is as follows. The effect is demonstrable in four hours and reaches a prolonged peak at about twenty four hours. At the end of about three days the effect is exhausted (Table 1). Thus, all time relations are extended to approximately five times the values shown by insulin in solution. This is accompanied, as might be expected, by a corresponding reduction in intensity of action. Judging by the degree of reduction in the blood sugar level, the peak effect of a single large dose of protamine zinc insulin is weaker to the extent of about 20 per cent of that of a comparable dose of insulin. Overlapping of effect of repeated daily doses increases the intensity of this effect, of course, which accounts for the tendency to fasting hypoglycemia, together with the fact that the peak effect of each single injection appears at about twenty four hours. Thus, the action of protamine zinc insulin may be epitomized as that of ordinary insulin stretched out to span about five times as much time with a five fold loss of intensity at any one time. The action of a single 60 unit dose of protamine zinc insulin is roughly comparable to that of five 12 unit doses given twelve hours apart, or sixty hourly 1 unit doses. The daily administration of 60 units of protamine zinc insulin accordingly, is roughly comparable to giving about 20 units of ordinary insulin every eight hours, or 10 units every four hours. In making use of this comparison it must be remembered that the scheme involves giving ordinary insulin at night as well as by day.

Use—Protamine zinc insulin has become invaluable as a means of providing sustained insulin effect with infrequent (once daily) injections. In mild diabetes where small doses are required, where the exact rate of insulin release is unimportant, and where insulin insensitivity is the rule control is most satisfactory. Even in severe diabetes where these features do not exist the degree of regulation of sugar balance is improved, wide variations are less violent than with or

particularly useful in mild diabetes when the postprandial sugar level is high but the fasting level tends to be proportionately lower. In these cases it is more likely to provide good control without nocturnal insulin shock than protamine zinc insulin.

Some clinicians have found other specialized uses of globin insulin. Used by separate injection along with protamine zinc insulin it controls some severe forms of diabetes efficiently.¹⁴ Used as an evening injection after ordinary insulin at breakfast and lunch it has given as good control as four doses of ordinary insulin daily.¹⁵ Both of these methods involve multiple daily injections of insulins, so cannot be considered ideal.

In severe diabetes the faults of globin insulin used alone stand out prominently.¹³ In large single daily doses it exhibits a decided tendency to cause late afternoon insulin shock. This may be prevented by afternoon feedings or by reducing the dose. However, in severe diabetes, even when the dosage is maintained at a maximum level, it is a serious fault of globin insulin that it often wanes so rapidly in effect that an overnight rise in the sugar level occurs, heavy glycosuria appears before and after breakfast, and doses large enough to reduce the level promptly are prone to cause afternoon insulin shock. Stated simply, in severe diabetes globin insulin as now manufactured fails to span the twenty-four hour period. In daily morning injections it fails to permit the overlapping effect so essential for good control. This is illustrated and compared with protamine zinc insulin in Period 3 of Table 2.

Thus, globin insulin is intermediate in time-activity between insulin and protamine zinc insulin, but its characteristics are too much like those of ordinary insulin and not enough like protamine zinc insulin. In gaining promptness and intensity of activity it has sacrificed the depot insulin effect to too great an extent. Its administration twice daily is much more efficient in severe diabetes, but again multiple injections are involved.

Another disadvantage of globin insulin as now manufactured is its tendency, like clear or acid protamine zinc insulin, to be variable in the rate at which it releases its insulin from one injection to another. Probably because of the fact that it depends for its sustained effect on partial precipitation after injection, the quick and slow component effects are somewhat too variable from dose to dose for greatest efficiency. As stated by Peck, acid or clear insulin modifications "seem more likely to dump out their insulin at odd moments and result in unexpected hypoglycemic reactions."¹⁶

PROTAMINE INSULIN MIXTURES AND MODIFICATIONS

Because of the failure of protamine zinc insulin and globin insulin to produce good control in single daily injections in severe diabetes there has been a great deal of study and clinical trial of protamine insulin modifications. Stimulated by Ulrich's early studies of mixtures of protamine zinc insulin and insulin-containing excesses of insulin,¹⁷ Colwell and his associates reported carefully controlled timing studies of various mixtures in 1942,¹ demonstrating that excesses of insulin are necessary to produce appreciable alterations in the effect of protamine zinc insulin. Subsequent studies showed these mixtures to be new protamine zinc insulin entities with accelerated time-activity.¹³ They indicated that a preparation containing about twice as much insulin as protamine zinc insulin and mixed thoroughly ("2:1 mixture") possesses the most desirable time-activity for injection each morning in severe diabetes. Contrary to popular belief, this preparation does not represent a mixture of the effects of the two insulins of which it is composed. It does not contain either insulin as such. When the two insulins composing it are mixed thoroughly a suspension of a new variety of protamine zinc insulin is formed. This compound, containing one-third as much protamine as standard protamine zinc insulin, is all present in precipitated form. It represents an insulin-saturated protamine zinc complex which, on injection, releases its insulin more rapidly during the first twelve hours than the second so that its effect is stronger than protamine zinc insulin during the day-time and weaker at night. It is therefore more likely to control post-prandial glycosuria and less likely to cause nocturnal insulin shock. Yet, even in severe diabetes its action usually is sufficiently sustained to control the fasting level and permit overlapping of daily morning doses.

In 1913 MacBryde and Roberts devised a somewhat similar modification of protamine zinc insulin¹⁴ in which the latter in precipitated form is suspended in a solution of insulin. It contains about 40 per cent as much protamine as protamine zinc insulin and is buffered so that about one-fourth of its insulin is in solution and three-fourths in the sediment. It was designed to duplicate the effects of insulin and protamine zinc insulin given by separate injection. Many clinical trials of it in its present form (designated "NP50") have shown it to possess the proper time activity for routine depot insulin therapy.¹⁵ Like the 2:1 mixture it largely eliminates the faults in timing of protamine zinc insulin and globin insulin and controls severe diabetes quite satisfactorily.

Action.—Careful clinical and laboratory comparisons of the 2:1 mixture and NP50 show them to be virtually indistinguishable in their time-activity.¹⁰ Both show unmistakably prompt reduction of sugar levels within four hours, attain their peak effect in twelve to sixteen hours after injection, wane in effect appreciably at twenty-four hours, but maintain sufficient activity in the second day after injection to permit desirable overlapping from dose to dose.¹ In these respects they are actually intermediate in effect between protamine zinc insulin and globin insulin (Table 1). Neither preparation is stable enough to meet rigid marketing specifications.

Use.—Although it may seem incredible that the timing properties of insulin modifications can be determined so accurately that fine points such as these can be demonstrated conclusively, it is a fact that they can. Although it might appear that the insulin requirements of different diabetic patients would vary so much that minor variations in timing are inappreciable, this does not seem to be true. Extensive clinical trial of the various depot insulins described shows a fairly uniform tendency of most severe diabetics to reflect both the too-prolonged and weak action of protamine zinc insulin and the too-intense and short action of globin insulin in poor control and health. Accordingly, these same patients transferred to appropriate doses of modifications with the characteristics of the 2:1 mixture and NP50 in single daily doses obtain better control and gain in health.^{8, 13, 19} Clinical application can demonstrate these facts easily in nearly all patients with severe diabetes.

As reasonably stable control is attained these patients show a tendency to strike even a better balance than the initial one in the course of a few weeks or months, provided the diet is constant. This "improvement in tolerance" is as striking in some patients as that seen in freshly treated diabetics who commonly show a sharp reduction in initial insulin requirement with successful treatment, although the improvement occurs at a higher insulin level and is seen as a more stable balance rather than as a reduction in insulin dosage.

THERAPEUTIC APPROACH

In diabetes complicated by acute illness only unmodified insulin with its prompt and dependable action is important. In routine therapy, however, acceptable methods of permanent regulation can be outlined as follows.

Diet.—Roughly one-half of all diabetics can be controlled satisfac-

torily by adjustment of the diet alone. When complications are absent and when insulin is not already in use it is considered good practice to attempt desugarization without the use of any insulin. Such a diet must meet the nutritional needs of the patient, of course, and must not be ketogenic in effect.

Protamine Zinc or Globin Insulin—When diet fails to accomplish desugarization, or when a submaintenance or ketogenic diet is the only one which will do so, the addition of one of the standard depot insulins is indicated in routine treatment of diabetes. This should be given in a single dose before breakfast each morning. The size of the dose depends first on the degree of glycosuria and hyperglycemia, and second, on the observed response of the individual patient. The latter must not be judged too hastily, especially with protamine zinc insulin, because overlapping and apparent accumulation of effect occurs for fully a week after daily doses are begun. For this purpose the morning fasting blood sugar concentration observed frequently is of the utmost practical importance. It provides the best possible measure of the degree of protamine zinc insulin effect.

When the fasting sugar level is high and the postcibal level is moderate, protamine zinc insulin is the preparation of choice. When the glycosuria following meals is heavy and the early morning sugar level is proportionately lower, globin insulin may be preferable, although this type of diabetes is unusual and usually responds to diet restriction. The effect of globin insulin may be judged more rapidly than that of protamine zinc insulin. In both cases the diet must be set at a maintenance level and must be constant. Diets high in carbohydrate are more difficult to balance with any form of insulin therapy.

Fully one half of all patients requiring insulin can be regulated satisfactorily by this simple procedure. In severe diabetes, however, difficulties which are characteristic of each of the standard forms of depot insulin may require the use of an insulin with more appropriate timing qualities. With protamine zinc insulin these difficulties appear in the form of excessive reduction of the early morning sugar level if the dose is great enough to control the glycosuria for the entire day. With less protamine zinc insulin the early morning level may be normal but glycosuria which may be heavy follows the meals. With globin insulin the reverse tends to occur. In dosage once daily amounts large enough to reduce the morning fasting sugar level to normal are likely to cause afternoon insulin shock. Correspondingly, less globin insulin may let the early morning sugar level rise too

high, because in moderate dosage it fails to span the twenty-four hour period in severe diabetes. The behavior of the patient reported in Table 2 (Periods 2 and 3) is typical of the inadequacies described.

Improved Protamine Insulin.—When any of these maladjustments occur they can be solved, as a rule, by the use of one of the modifications of protamine zinc insulin with accelerated action, in once-daily morning dosage. The most convenient of these improved depot insulins is the "2 1 mixture" described above. It meets the timing needs of most severe diabetics, provided the diet is moderate in carbohydrate content (carbohydrate to fat ratios of 1 1 or 3 2 in grams). Such an insulin preparation in appropriate dosage ordinarily clears or reduces the postcibal glycosuria without causing insulin reactions, and holds the sugar level at normal or moderate levels throughout the night without hypoglycemia. It tends to avoid both the daytime glycosuria occurring with protamine zinc insulin and the noon or afternoon insulin shock so frequently caused by globin insulin.¹ Likewise, it is less likely to cause nocturnal insulin shock than protamine zinc insulin and holds the early morning sugar level down better than globin insulin (Period 4, Table 2).

Mixtures containing less insulin than the 2 1 mixture are rarely indicated. There is some acceleration of action when 1 1 proportions are exceeded, but it is scarcely of practical importance.¹ In a large series of severe diabetics it has been possible to shift directly from protamine zinc insulin to a 2 1 mixture when needed, without a single indication for a preparation intermediate between these two.²⁰ In a small proportion of cases showing poor balance with protamine zinc insulin or globin insulin it has been useful to "sweeten" the 2 1 mixture by small further additions of insulin up to 2½ 1 or 3 1 proportions. A few patients have been regulated better on one of the mixtures given twice daily. Some "brittle" patients cannot be regulated chemically at all. However, even these difficult cases seem less violently unstable when using accelerated protamine insulins than when using orthodox preparations, with the exception of ordinary insulin in frequent injections.

The improved control seen with the 2 1 mixture can also be obtained with other modifications less readily accessible. The preparation known as "NP50" has been described previously. Peck has recently reported a suspension of crystalline protamine insulin with time action comparable to the other efficient modifications.¹⁶ Doubtless globin and histone insulins could be modified in such a way as to reproduce the activity shown to be the most desirable. Any prepara-

tion designed for this purpose should be planned so that it can reflect small further additions of insulin, for the benefit of the small group of patients in which even more prompt and intense action than that produced by the 2 1 mixture is desirable

TABLE 2

EFFECTS OF VARIOUS DEPOT INSULINS IN SINGLE DAILY DOSES IN SEVERE DIABETES MELLITUS*

Day	Insulin Units	Urinary Sugar					Blood Sugar (fasting)		Remarks
		Noon	Aft.	Eve.	Morn.	24 Hour Vol Gm			
Period 1 Quantitative diet only C-160 N-75 F 106 Cal. 1891 G 214									
1	0	++++	++++	++++	++++	2600	62.2	276	
2	0	++++	++++	++++	++++	2160	38.0	251	
3	0	++++	++++	++++	+++	2200	31.7	260	
4	0	++++	++++	++++	++++	2010	41.2	233	
5	0	++++	+++	+++	+++	2320	39.6	246	
Period 2. Protamine zinc insulin added in one daily dose before breakfast									
6	40	++++	+++	+++	+++	2020	30.5	212	
7	40	++++	+++	+++	+++	1660	21.8		
8	40	++++	+++	+++	+	1160	11.1	118	
9	40	+++	+	+++	0	1200	14.4	87	
10	40	+++	++	+++	0	1640	15.8	63	Reaction at 7 A. M
11	40	+++	++	++	0	1600	12.6	70	Reaction at 7 A. M
Period 3 Protamine zinc insulin stopped and globin insulin started									
12	40	+	0	0	0	910	4.0	102	Reaction at 5 P. M
13	40	++	0	0	0	1180	7.3	170	
14	40	+++	0	+	++	1080	10.9		
15	40	+++	0	0	++	1300	9.2	192	Reaction at 4 P. M
16	40	+++	+	0	+	1820	12.2	206	
Period 4 Globin insulin stopped and 2 1 mixture started									
17	40	++++	+++	++	++	1900	21.0	172	
18		+++	++	++	0	1260	3.8	140	
19	45	+	0	0	0	910	1.5	126	
20	40	0	0	0	0	1160	0.4	90	
21	40	0	0	0	0	1580	0.5		
22	40	+	0	0	0	1160	0.4	104	

* 1 male diabetic patient, age 23, weight 112, former weight 135 typical symptoms of three months duration. No previous treatment.

In this connection it is important to realize that the introduction of an improved insulin of this type does not necessarily mean an addition to the number of insulin preparations now marketed. If its timing and stability characteristics are worked out carefully it can not only satisfy the requirements in severe diabetes where both protamine zinc insulin and globin insulin are inefficient, but it can also replace

both protamine zinc insulin and globin insulin in mild diabetes where details of timing are unimportant. Wide clinical experience in the hands of many skilful observers has demonstrated that a stable preparation with activity intermediate between the two standard depot insulins now available can replace both of them and make extemporaneous modifications unnecessary except for a small proportion of the patients in which it is now indicated.

SUMMARY

An insulin which need not be administered more often than once daily is indispensable for routine treatment of diabetes mellitus. Protamine zinc insulin must too often be supplemented by the use of another insulin for good control. Globin insulin fails to permit the overlapping of effect from day to day which is so essential in severe diabetes. Preparations which are intermediate in timing between these two commercial varieties can be prepared. They have been demonstrated to be efficient in controlling severe diabetes incapable of good control by either protamine or globin insulin used alone. Furthermore, they can be shown to control mild diabetes fully as well if not better than either of the commercial preparations now available. There is good agreement between practically all students of the problem as to the ideal timing characteristics which are required. Such a preparation is best improvised at present as a "2/1 mixture." It is hoped that a stable insulin of this type will be marketed and that it will replace the two less efficient depot insulins now in use.

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INSULIN MIXTURES AND MODIFICATIONS

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A MAJOR problem in insulin therapy that developed between the years 1922 and 1936 was how to control the blood sugar level in the fasting condition, a contingency that arose in spite of the use of multiple daily injections of insulin. Nocturnal control was finally accomplished through Hagedorn's discovery¹ that the action of insulin could be modified and extended by combining it with certain protein precipitants, namely the protamines, histones, kryn and globin. Protamine was finally chosen as the substance most likely to be useful clinically and after the role of zinc had been more fully elucidated by the Toronto group,² its incorporation into the combination resulted in the ultimate marketing of standard protamine zinc insulin as now available. The great contribution of protamine zinc insulin to the control of diabetes lies in its peculiar attribute of controlling the nocturnal blood sugar level. This gain must never be sacrificed.

But protamine zinc insulin too has projected new problems. With it, individual readjustments of the patient's habits of eating, alterations in the percentage distribution of the dietary, and abnormal spacing of meals and intermeal feedings have been resorted to in attempts to conform the individual's metabolic load with the time-activity of protamine zinc insulin. The patient's life again had to be readjusted to fit the pharmacology of the insulin preparation. In spite of this there has remained a group of severe cases requiring multiple doses of insulin and protamine zinc insulin before both daytime and nighttime control can be successfully established. Recourse has, therefore, been had to modifications of insulin having varied rates of onset and durations of action. Rather than readjustment of the patient's conditions to fit the action of the insulin, the attempt has been made to prepare insulin modifications which fit the average needs of the patient. This signifies another new step in the progress of therapy—an opposite approach to the problem. Much progress has been made in this direction.

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It is important in this connection, first, that the availability on the market of a large number of different preparations not add to the complexities of treatment of the great mass of diabetic patients by physicians who are not and cannot be expected to become experts in this field, and, second, that the nocturnal control which was gained only after years of painstaking investigative efforts be not inadvertently lost by too enthusiastic and ill-timed adoption of some preparation whose pharmacologic properties are not ideal. This would be bound to happen with the general adoption of any modification having an effect averaging less than twenty-four hours in duration. It seems generally agreed that the action of globin insulin (with zinc) is too short, averaging about sixteen hours. The ideal preparation must act long enough to provide some overlapping from day to day or it will neither provide enough insulin activity to metabolize a normal sized breakfast, nor will it prevent nocturnal hyperglycemia. To put it more popularly—the overlap is what “saves the day.” The overlap is what Joslin has aptly termed “insulin insurance from one day to the next.”

DEVELOPMENT OF METHODS

The early development of the technic of mixing insulin and protamine zinc insulin, as well as all the present employed methods of modifying insulin, were the direct outgrowth of early experiments conducted by Hagedorn and his colleagues³ at the Steno Memorial Hospital. Subsequent attempts to combine standard preparations in order to obtain effects that were intermediate in action were described^{4a} and a follow-up report^{4b} was made on more than two years of clinical experience with extemporaneous mixtures in a group of 150 cases. Mere numerical additions to this group would be repetitious. It was concluded that the 2.1 (insulin to protamine zinc insulin) mixture was the most generally useful (70 per cent of cases). In addition, comparisons in groups of patients were made between certain other special modifications and mixtures, both freshly prepared and premixed, and the conclusion was reached that the degree of clinical improvement noted with the 2.1 mixtures as advocated by Colwell⁵ and the specially modified protamine zinc insulin, type NP50,^{*} as reported on by MacBryde⁶ was for practical purposes equal (Fig 46). It is granted that the action of these two combinations may not be identical, but their differences in clinical effect are not par-

* A buffered specially modified protamine zinc insulin combination made from 0.5 mg of protamine per 100 units of insulin instead of the standard 1.25 mg of protamine per 100 units.

ticularly significant. While the average blood sugar levels under treatment with type NP50 may be slightly lower in this group of patients, the general character of the curve obtained with the 2 1 mixture was smoother and subject to less periodic variation, and both curves are certainly within quite normal limits

Since 1944, both in hospitalized cases and in outpatients of the Indianapolis series, the deliberate substitution of one of these preparations for the other has been repeatedly and continuously brought about, with no practical difficulties and without significant gains or losses in the level of control. Furthermore, we have continued to

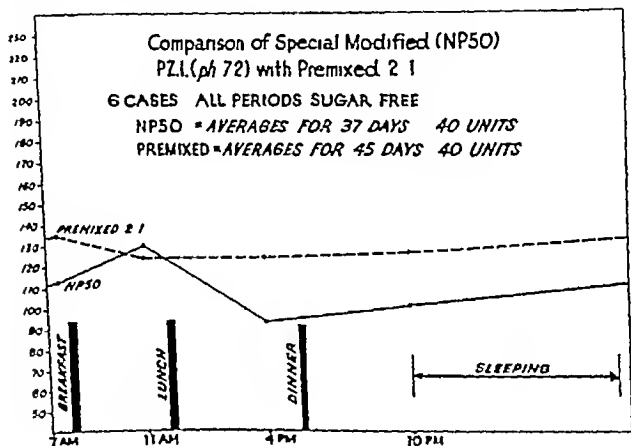


Fig. 46.

treat patients routinely by means of a single injection before breakfast—usually of a mixture made in the syringe prior to injection, and in most instances with the 2 1 (insulin to protamine zinc insulin) mixture. The only difference in the subsequent experience has been that by elimination of the group of cases using mixtures made from less than the 2 1 ratio the proportion of cases now taking 2 1 combinations has enlarged still further. Colwell's more recent experience⁷ in treatment of a group of 150 severe cases with 85 per cent of the group classified as improved is confirmed by Sprague⁸ with 87 per cent of cases taking 2 1 to 3 1 mixtures.

RECENT PROGRESS

Over the past several years a large series of different modifications having various time-activities has been studied. Some of the more promising of these combinations have been subjected to limited clinical trial by a group of competent clinical investigators, others have not shown sufficient advantage in preliminary clinical usage to justify their release for wider study. Sufficient experience is at hand to justify some general conclusions based on personal clinical experience with them, the comparative studies made on animals in the Lilly Laboratories, plus the accumulated experience of cooperating clinical observers as reported to me. These conclusions are that

1 The acid (clear) series of modifications studied thus far require about twice as much of the modifying agent in order to act as long as the neutral (buffered and precipitated) series

2 The members of the acid (clear) series thus far studied have been more variable, more erratic and more unpredictable in their effects than comparable members of the neutral series. They seem more likely to "dump out" their insulin at odd moments and to result in unexpected hypoglycemic reactions

3 The behavior of these modifications is apparently regulated as to onset and duration by the content of the modifying agent in relation to the insulin content, by the pH and buffering, and by the metal used with the agent. Some unexplained factors also seem to influence the solubilities of certain compounds in water and serum

4 The most generally useful combinations studied thus far are the 2:1 mixtures and type NP50, which seem to occupy the same general zone of time-activity. Both preparations seem capable of improving the level of control in the majority of diabetic patients, when given once daily before breakfast. (In certain individual instances, however, another combination, e.g., 2:5:1 or 3:1 or rarely 3:2 may give better clinical results.) The type of action exemplified by either of these products approaches most closely to the ideal desired. Either preparation appears capable of meeting the normal physiologic needs of the average diabetic patient by providing sufficient insulin to meet day-time requirements and a long enough duration of action to maintain proper levels in the fasting state, since both provide moderate overlapping effects

5 There is divided opinion regarding the feasibility of treating patients by means of mixtures extemporaneously made in the syringe just prior to injection. The points usually emphasized by opponents of the method are that the procedure is complicated, that there is greater

likelihood of variability in dosage and response, and more hazard of error in making the mixture. Against these arguments are the fact that it is unlikely that any one insulin preparation will ever be found to meet the needs of all patients, that such mixtures are adjustable to the individual needs of all patients and that their use avoids the necessity of marketing additional new modifications with attendant confusion and duplication of stocks.

Obviously if one wants to use the mixture procedure successfully, it is necessary to teach the hospital resident and nursing staff, and make some provision for routine teaching and periodic check-ups of the patient's technique. There is also an occasional patient who is unsuitable for one reason or another.

6 The use of an oversized vial containing 10 cc. of insulin, to which may be added the desired amount of protamine zinc insulin to prepare a bulk mixture is well suited to the use of special clinics, but does not seem well adapted for general use by patients. Some observers have obtained excellent results with this method. Palmer⁸ recently reported on his two-year experience, 25 per cent of the patients on mixtures were better controlled when the insulin mixture was thus prepared in bulk rather than in the syringe. Holcomb⁹ and Woodyatt¹⁰ have also had favorable experience with this procedure. Undoubtedly it does facilitate comparisons by elimination of possible variability in the mixture, but there is the added risk of infection should contamination occur. Furthermore, some capable person must be trained to make the mixture properly.

7 There are certain difficulties in the large scale production of a 2:1 mixture and NP50 which are still not solved. Standardization of different large scale batches made in different laboratories, and long-term stability are problems of considerable magnitude but probably not insurmountable.

SOME CHARACTERISTICS OF MIXTURES AND OTHER MODIFICATIONS

There is still some disagreement as to the mechanism by which the desirable action of certain mixtures and special modifications is brought about and much of this may be attributed to the different conditions under which various investigators have worked. Ulrich¹¹ measured centrifuged precipitates obtained from mixtures of standard products. Colwell⁶ has employed chemical methods for determination of the "excess" insulin in supernatants and Peck⁴ attempted to translate into clinical terms of units of quick and prolonged action.

the results obtained from animal assays of buffered combinations having the same ingredients as extemporaneous mixtures. It was emphasized that these figures were only approximate and did not necessarily imply that the time-activities of either the quick-acting or the precipitated components were identical with those of Insulin USP and Protamine Zinc Insulin USP as marketed

There is another aspect of the problem that should be noted, namely that all these different combinations are pharmacologically active not in the water solutions in which they have been studied, but in the body fluids. Their effects must be modified *in vivo* by their dispersion in the protein-containing tissue fluids. The effect of blood serum, for example, in altering the solubilities of several different modifications is cited to emphasize the importance of the tissue fluids in modifying the rate at which the active principle is released. Bang,¹² working in the Steno Memorial Hospital, presented evidence that the splitting of protamine insulin is an enzymatic process, and that the active enzyme is probably of the kathepsin type. Zinc is believed to act as an enzyme inhibitor, which explains the slower effect of protamine zinc insulin. In earlier publications of Hagedorn¹³ some experiments by his colleague Krayenbuhl are described to throw further light on the nature of the protamine insulin combinations. Increasing quantities of protamine were added to equal volumes of insulin solution, and each of the clear centrifuged supernatants then divided into two tubes. To the clear fluid in each series of tubes an equal quantity of insulin and of protamine were then added, respectively. Turbidities were read in the nephelometer, and the reciprocal values plotted as function of the amount of protamine. The curves intersect at a point which is termed *isophane* to signify the appearance of an equivalent precipitate on addition of either the insulin or the protamine. Compounds corresponding to this point are called *isophane compounds*. All other proportions of insulin and protamine zinc insulin are called *heterothane*, and contain a surplus of insulin or of protamine. If insulin or protamine is present in the supernatant, the addition of protamine or insulin, respectively, will cause formation of a precipitate invisible macroscopically, but detectable by nephelometry. Hagedorn pointed out that the *isophane* compound did not have the maximum prolongation of effect, but on the other hand could be mixed with insulin to make *heterophane* compounds with surplus of insulin.

The following experiment is of interest in this connection. At pH 7.2 the several preparations were centrifuged, and the clear supernatant

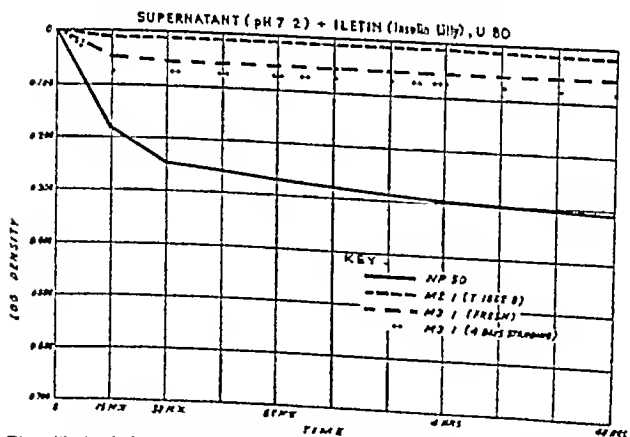
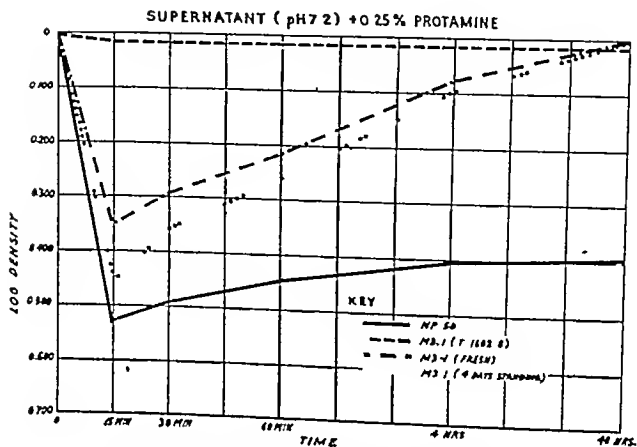


Fig 47—Turbidities of identical supernatants when treated with protamine (above) and insulin (below)

liquid divided into two tubes. To one tube was added a solution of 0.25 per cent protamine (Fig 47, A), and readings taken of the turbidity (Evelyn F620) at the times indicated. In the case of the 2:1 mixture (T-1662-8) there was but little change, indicating the virtual absence of insulin in the supernatant. A striking turbidity developed in the tube containing type NP50, however, while the alteration in the case of the 3:1 mixture, both when freshly prepared and after standing four days was intermediate between the two. To each of the other series of tubes was added an insulin solution with findings somewhat similar but not as pronounced (Fig 47, B). These results indicate that the 2:1 mixture is very close to the isophane ratio as it contains neither excess of insulin or of protamine. Animal assays have shown the presence of insulin in the supernatant from type NP50. Colwell⁶ maintains that the 2:1 combination represents a specific entity differing from the other mixtures commonly employed.

The quantitative differences between the ingredients insulin and protamine in a 2:1 mixture and in type NP50 are slight. The former contains 0.42 mg of protamine per 100 units of insulin, while the latter is prepared with 0.5 mg of protamine per 100 units of insulin. The mixture is at approximately pH 5.6, but type NP50 is buffered at the time of preparation to pH 7.2. Clinical trials were, therefore, made of another special modification, type NP42, which differed from the 2:1 mixture only in pH (7.2). The comparisons disclosed an excessive number of hypoglycemic reactions, usually about 11 A.M., and indicate too abrupt action in the early hours after injection.

CRYSTALLINE PROTAMINE INSULIN, TYPE NPC50

In previous reports I have called attention to the questionable stability of certain of these newer modifications, and in addition there are factors which would make standardization of the products of different manufacturers a difficult problem. With the permission of Dr. Hagedorn, the following preliminary clinical data are presented on still another specially modified preparation which is designated type NPC50. In this code, the "C" refers to crystals of protamine insulin which have been formed under conditions described by Krayenbuhl and Rosenberg,¹⁴ co-workers of Dr. Hagedorn. They are described as beautiful tetragonal crystals with shiny faces and sharp smooth edges, and are extremely stable under proper conditions but change rapidly in the presence of serum. They are of especial interest in view of the fact that they form in isophanous conditions,

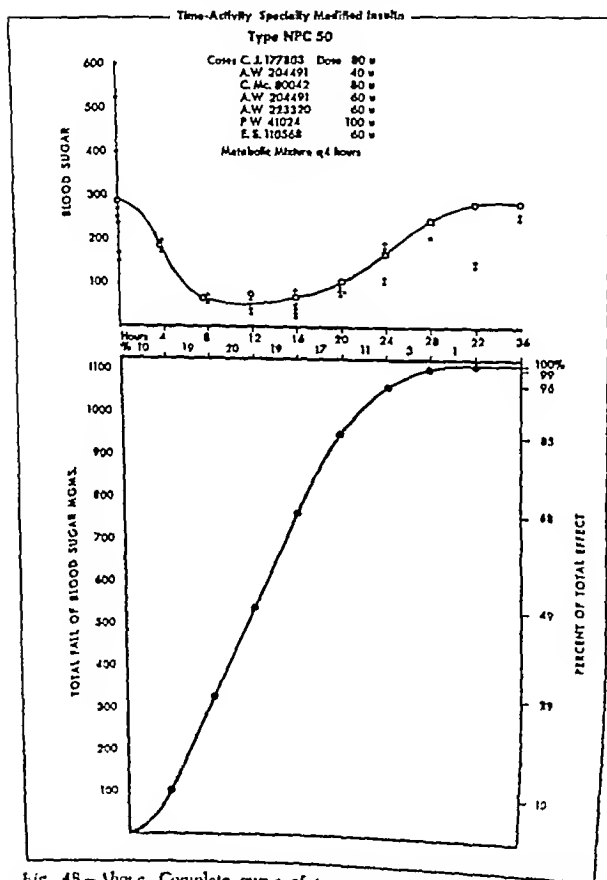


Fig 49—Above Complete curve of time-activity based on averages in six cases. Below These data are transformed into a cumulative curve to show per cent of action in each four hour period

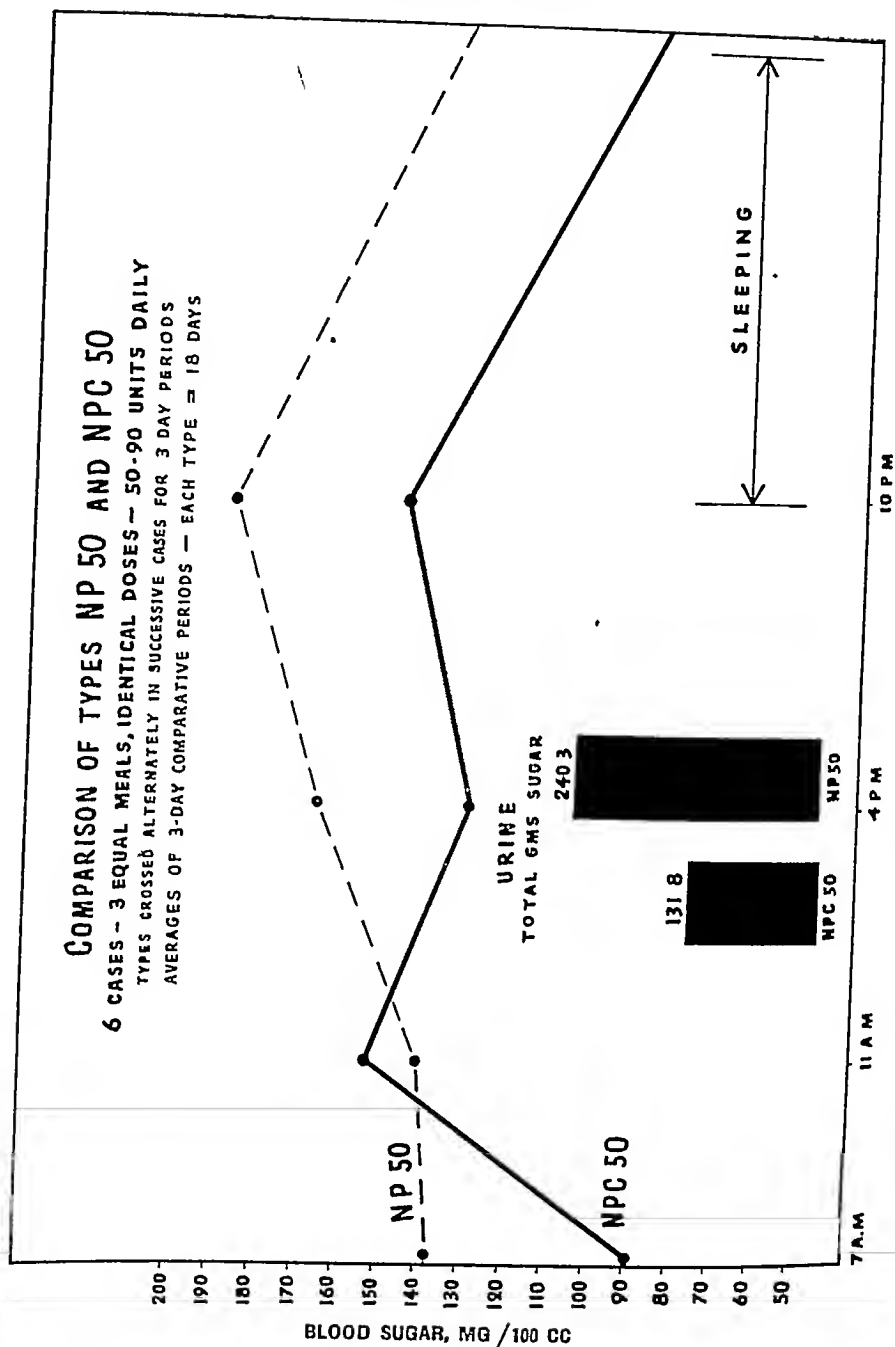


Fig 49

and make possible the preparation of combinations to which may be added desired quantities of insulin. Furthermore, the proportion of protamine to insulin used in this particular formation was 0.5 mg

of protamine per 100 units of insulin—a proportion that on extensive clinical trial has worked out satisfactorily in the case of type NP50

These data are very preliminary and too meager to warrant conclusions, but the results of recent clinical studies are encouraging. Figure 48 illustrates some time-activity curves and a composite of them, calculated in per cent of action in four-hour periods. Type NPC50 appears to be very slightly less active in the first four hours than M2 1 and type NP50, having a fairly even and sustained action (17 to 20 per cent) during each of the four succeeding four-hour periods, and total duration of action of approximately twenty-eight hours. The present series represents diabetic cases of severity, and the inclusion of data obtained in milder cases, with lower doses, will, of course, influence the rate of onset and duration of action.

A clinical comparison is shown in Figure 49. Thus far the results of treatment with type NPC50 seem similar to those obtained with type NP50, except for the lower level fasting, which is a reflection of the slightly longer effect, and these results, as shown previously, do not differ materially from those following treatment with a 2 1 mixture. A great deal more data will have to be accumulated before any final conclusion can be reached.

EXTEMPORANEOUS MIXTURES

Pending the general adoption and ready availability of a specially prepared modification or mixture having the most desirable attributes, it is feasible to employ mixtures of standard insulin and protamine zinc insulin which are made in the insulin syringe just prior to injection.

The method of readjustment of the hospitalized patient to a single injection admixture is outlined in Figure 50. In the uncomplicated case or in the outpatient department, treatment may be started directly by prescribing 9 to 21 units of a 2 1 mixture which dose is then revised upwards or downwards depending upon the response. In most hospitalized cases, however, there is an early period of several days after admission during which a complication is present, with consequent fluctuation in insulin requirement necessitating daily or even hourly revision in insulin dosage. It is only after conditions become reasonably well stabilized that any regimen depending on a tolerably even balance between insulin requirements and metabolic load should be undertaken.

The single injection is always given before breakfast each morning. The size of the dose of protamine zinc insulin is determined by the

conditions in the *fasting state* and the amount of insulin is regulated by the conditions during the *daytime (feeding)* hours. Glycosuria and hyperglycemia following meals calls for more insulin whether it is being given separately or as one component of a mixture. If both the fasting and postprandial blood sugar levels are too low, a reduced dosage is indicated. If both periods are poorly controlled the total amount of the 2:1 mixture is increased, while if the fasting levels are too high a greater proportion of protamine

METHOD

Recent cases and those not previously treated

- I (a) First day—(10) units Protamine Zinc Insulin
- (b) Increase daily by (5) to (10) units until urine is nearly sugar-free on arising, or until blood sugar (fasting) approaches normal levels

II If glycosuria and hyperglycemia persist after meals ← II

Add supplementary doses of Insulin (varying with Benedict test)

e.g.

YELLOW
5 units

ORANGE
10 units

RED
15 units

III Replace multiple injections with single-dose admixture.

- (a) Replace total with 2 (1) mixture
- (b) If daytime glycosuria and hyperglycemia persist, increase insulin content, e.g. 2 1/2 (1); 3 (1)
- (c) If postabsorptive (fasting) glycosuria and hyperglycemia, increase amount of Protamine Zinc Insulin in mixture, e.g. 3 (2)

The criteria for adjustment of admixture are identical with those governing separate doses.

*Protamine Zinc Insulin denoted by circle. Ratio of mixture e.g. 2:1, refers to parts of Insulin and Protamine Zinc Insulin in terms of units. Mixtures are always prepared from preparations having the same concentration.

Fig. 50—Method of readjustment of the hospitalized patient to a single injection admixture

zinc insulin is needed in the mixture. Most cases require between two and three times as much insulin as protamine zinc insulin in making a mixture. In exceptional cases some further readjustments may be necessary, particularly during infections, when the usual course is to supplement the mixture with unmodified insulin doses given separately.

The admixture of insulin and protamine zinc insulin is a technique that is easy to do but difficult to explain. *Patients must be actually*

shown how to make their mixtures The new feature to be learned is how to draw an air bubble into the syringe and roll it through to mix the doses The dose of insulin is always drawn into the syringe first, then the protamine zinc insulin up to the total (so the patient does not have to calculate) Since all the daily doses are combined into one injection, the 80 unit per cubic centimeter concentrations are usually preferable in order to lessen the volume. Preparations of the same manufacturer should be used in order to keep conditions as constant as possible. In this connection, however, one need not be concerned about the effects that may be produced by an error of a unit or two in either direction, since it is obvious that one is working within a fairly broad zone of activity and the quick effect is not identical with the effect of unmodified insulin Owing to the large doses sometimes given, a 2 cc. capacity syringe calibrated for 80 and 160 units has been developed

Suppose the dose is to be 30 units of insulin and 15 units of protamine zinc insulin (2:1 mixture) The total is 45 units This mixture might be made from either U-40 or U-80 insulin and from protamine zinc insulin containing either 40 or 80 units per cubic centimeter Use only one concentration or the other Do not attempt to mix different concentrations together The bulk of large doses should be reduced to 1 cc. or less wherever possible by using the 80 unit per cubic centimeter products First withdraw the clear insulin up to the 30 unit mark in the manner described, then draw into the syringe enough protamine zinc insulin (15 units) to complete the dose, up to the 45 unit mark. Always withdraw the clear insulin first as it will not matter if a drop of it enters the vial of protamine zinc insulin However, if a small amount of protamine zinc insulin gets into the vial of insulin, it will cause the clear insulin to become cloudy Carefully follow each step of the method outlined A little practice with the two used insulin vials which have been filled with water will increase proficiency and accuracy in this technique.

SUMMARY

1 Nocturnal control of hyperglycemia is a function of long acting modifications of insulin and is gained at the expense of rapidity of onset of action The ideal preparation should act long enough to maintain the level of blood sugar fasting and should possess moderate overlapping effect to compensate for the lack of immediate rapid action This permits control of both daytime and nighttime periods Studies of a large series of modifications indicate thus far

that the 2 l mixture and specially modified protamine zinc insulin, type NP50, both meet these requirements in the average case. Neither of these preparations is as yet well suited for large scale production

2 Preliminary data suggest that a specially modified protamine insulin, type NPC50, containing crystals of protamine insulin formed under isophanous conditions, may aid in solving some of these problems

3 Pending general adoption of a new modified insulin preparation having attributes which make it likely to improve or simplify the management of the average case, it is practical and effective to employ mixtures of insulin and protamine zinc insulin which can be individually prepared in the insulin syringe and adjusted in timing to fit the needs of the individual case

ACKNOWLEDGMENTS—The author is greatly indebted to the cooperating clinicians who cannot be named individually, to Dr George B Walden, Head, Biochemical Research Department, who supplied the modifications and whose counsel and advice through the years has been invaluable, to Miss Helen Kottowski for the innumerable blood sugar determinations, to T Woodmansee for performing the nephelometric studies, to the Resident Staff of Indianapolis City Hospital and the Lilly Unit for continuous wholehearted cooperation, and finally to certain patients whose willingness to subject themselves to multiple punctures day after day surpasses all understanding

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UNUSUAL REQUIREMENTS FOR INSULIN

Resistance, Refractoriness, Insensitivity to Insulin

MARTIN G. GOLDNER, M.D. *

WIEN, thirty years after Mering's and Minkowski's discovery that total pancreatectomy in the dog produces diabetes, Banting and Best succeeded in demonstrating the hormone of the pancreatic islet cells, many physicians may have felt that the problem of diabetes was solved. Organic disease of the pancreas seemed to be its cause, and insulin therapy the substitution for a pathologically decreased hormone production. It is worth while to remember that, even now, twenty five years after the discovery of insulin, the cause of human diabetes is still unknown. Human diabetes is not a surgical diabetes, and insulin requirement does not always reflect the degree of islet cell impairment. Indeed, not infrequently, no pathological changes are found in the pancreas of patients who die with severe diabetes. Next in importance, to suggest that diabetes may be more than an organ disease of the pancreas, is the phenomenon of insulin resistance.

The term "insulin resistance" is used commonly to describe a condition in which an unusually large requirement for insulin exists. "Insulin refractoriness" or "insensitivity to insulin" are used occasionally as synonyms for insulin resistance. None of these terms is intended to imply an etiological mechanism. Since, as will be shown, in many instances the cause of insulin "resistance" is unknown, and in others it is neither "refractoriness" nor "insensitivity," it may be more appropriate to speak simply of "unusual insulin requirement," as proposed by Pollack.¹

What is an unusual requirement for insulin? The best definition seems to be the following: an unusual requirement for insulin exists when the need for insulin is greater than in "total diabetes." By "total diabetes," we understand the state after total pancreatectomy. In other words, if an individual requires more insulin than a normal pancreas can be expected to produce, a condition of "unusual" insulin requirement is present.

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THE PHYSIOLOGICAL AND THE UNUSUAL INSULIN REQUIREMENT

So long as we have no method to determine the insulin content of the blood, no direct estimation of the daily insulin production is available. It is likely that the rate of secretion fluctuates widely and therefore our knowledge of the insulin content of the pancreas itself (2 to 4 units per gram) is of no value for our problem. An indirect method is the estimation of the insulin requirement in total diabetes. Until recently, such estimations had to be based on observations of depancreatized animals, and varied between 20 and 200 units of insulin per day^{2a, b}. The modern development of surgery has made possible the extirpation of the pancreas in man as treatment for pancreatic malignancy, and has given us the opportunity to observe the carbohydrate metabolism in such patients. Several cases are on record in the literature and, much to the surprise of all observers, it was found that none of these individuals required more than 40 units of insulin per day on a normal carbohydrate intake^{3a, b, c, d, e}. Conclusive as these findings seem to be, they are only of recent date, and further observations will be needed to give final proof. It should be mentioned, however, that they are in line with indirect evidence of earlier clinical observations. Joslin⁴ reports that his "severest" diabetic patient (Case 1542) could be controlled on a carbohydrate intake of 140 gm with 42 units of insulin, and another of his patients (Case 8194) whose pancreas at autopsy weighed only 15 gm, was regulated for some time with 80 units daily. Similar reports of rather moderate insulin requirements, in view of almost complete destruction of the pancreas by inflammatory or neoplastic processes, are scattered throughout the world literature.^{5a, b, c, d} We may, therefore, assume that 40 to 80 units of insulin are sufficient to maintain normal carbohydrate metabolism in the absence of the pancreas. In other words, such an amount of insulin appears sufficient to substitute for the daily insulin secretion of a normal islet cell apparatus. Any need for excess insulin will manifest itself as "decreased sensitivity," "resistance," or an unusually high insulin requirement. Since, in such cases, the insulin deficiency exceeds the physiological insulin supply, it is evident that it must have extraneous causes beyond any possible islet cell impairment.

EXTRAPANCREATIC CAUSES OF INSULIN DEFICIENCY

Theoretically, any deficiency state may be due to one or more of the following three possibilities: (a) Underproduction (b) Increased demand (c) Faulty utilization. Faulty utilization may be the result

of any process in the periphery which renders a normal product ineffective or destroys it, or it may be caused by faulty production, dysfunction. Since there is no evidence for dysfunction of the pancreas in the case of insulin deficiency, we may neglect this last theoretical possibility. It can easily be understood that, except in underproduction, the degree of deficiency is a direct function of the demand for insulin, and varies with it. Thus the deficiency may still be increased even when the production is exhausted completely. In our particular problem, we have seen so far that underproduction and exhaustion of the islet cell apparatus does not explain the case of unusually large insulin requirement. We, therefore, have to discuss those factors which either impose an increased demand or render insulin ineffective in the periphery, and thus cause faulty utilization. Let us consider each condition separately. It will be worth while to keep in mind that, in this context, we are concerned not only with mechanisms which are known to be diabetogenic, but also with those factors which can be shown to enhance an existing diabetic state.

1. Increased demand for insulin occurs whenever the rate of gluconeogenesis or glycogenolysis is increased and glucose oxidation in the periphery is delayed. Hyperfunction of the extrapancreatic endocrine mediators of carbohydrate metabolism, the pituitary, the adrenals and the thyroid, is known to produce hyperglycemia.⁶ This hyperglycemia is due at least in part to increased protein catabolism with subsequent increased gluconeogenesis. In the case of the pituitary, it is well known that treatment with extract of the anterior lobe not only enhances preexistent hyperglycemia and glycosuria, but precipitates the development of diabetes in a susceptible normal experimental animal. The other endocrines, when hyperfunctioning have been shown to enhance diabetes.

Increased protein catabolism is present also after injuries of any kind as for instance fractures or operations, and in infections. It is at least suggestive experimental evidence that the increased insulin requirement in infections is due entirely or in part to this mechanism.⁷ The liver is not only the passive storehouse of glycogen but takes part actively in carbohydrate metabolism. Any impairment of its functions, as for instance delayed glycogenesis and increased glycogen breakdown, will result in a hyperglycemia which is resistant to insulin.⁸ And indeed, unusually large insulin requirements are not infrequent in diabetics with liver disease.

All these mechanisms manifest themselves by hyperglycemia. The question may arise whether hyperglycemia by itself—for instance

alimentary hyperglycemia—may call for unusually large doses of insulin. It is not yet established whether or not overfeeding with glucose alone is diabetogenic, on the other hand, excessive glucose intake will certainly enhance the diabetes, though clinically the insulin requirement in such instances seems to remain within physiological limits. This makes it likely that, in the above mentioned conditions, the hyperglycemia is only a sign of increased insulin deficiency, and not the primary cause.

2 Insulin deficiency due to faulty utilization, or inefficiency of insulin, is seen in cases of immunity to insulin, rapid destruction in the periphery, and poor absorption. Insulin is a protein body and, as such, is capable both of forming antibodies and of being destroyed by proteolytic processes.

It has been shown that insulin is inactivated *in vitro* by protein splitting ferments such as trypsin.⁹ Experiments *in vivo* have been inconclusive, but it seems permissible to assume that, where the tryptic activity of the blood is stimulated as, for instance, in infection, insulin may be destroyed more readily. This may be another factor in the increased insulin requirement of infections. It also has been shown that blood cells, erythrocytes and especially leukocytes inactivate insulin,^{10a, b} probably by proteolysis. The recent report of a case of insulin-resistant diabetes complicated by leukemia may belong in this category.¹¹

Antibodies to insulin have been demonstrated by several authors.^{12a, b, c, d} Though insulin is only a weak antigen, and insulin immunity is a rather rare condition, it is significant that positive immunological tests have been obtained in just those patients who showed some of the highest insulin requirements ever reported. Development of insulin immunity is probably also the cause of the ever-increasing insulin doses which are required occasionally in the shock treatment of schizophrenia.

Again we wish to emphasize that we are speaking here, not of diabetogenic mechanisms, but of factors which increase insulin deficiency. It is quite likely that only commercially prepared insulin, and not the body's own insulin, is able to produce antibodies. Hence, insulin immunity may not be a cause of diabetes, though it may raise the insulin requirement to unusually high levels.

The two following conditions of faulty utilization of insulin occur only in patients who are under insulin treatment. Not infrequently "insulin-resistance" is diagnosed when, in reality, the patient is sensitive to insulin, but insulin does not reach its place of action. This

happens in cases of poor absorption and faulty administration. An example of the former is edema. If insulin is injected into edematous tissue, its absorption will be delayed. It may remain as an inactive depot at the place of injection and cause foreign body granulations, or may be destroyed in a short period of time; in any case, it does not fulfill its function, and ever-increasing doses of insulin may be required.

By faulty administration, we mean the frequent injection of insulin at the same site. Like any chronic traumatization, frequent injections at the same site will call forth connective tissue granulations and scarification. Such areas lose their normal vascularity and, the poorer the blood supply, the poorer the insulin absorption and utilization. One may argue whether such cases should be included here, since evidently their true insulin requirement is normal. We feel that special emphasis should be given to this mechanism of "pseudo-resistance" because of its great practical implication. Cases of this kind which occur not infrequently could easily be avoided, so long, however, as their true cause is not seen, they will be regarded as cases with unusually high insulin requirement, like any of the other groups.

Recently, a 17 year old diabetic girl was sent to our clinic with a diagnosis of insulin resistance; her daily insulin requirement had risen to four hundred units. Simple inquiry and inspection revealed that, for months, she had taken her injections into two small areas on the outer surface of her thighs, and marked induration had developed in these areas. Change of the site of injection reduced the insulin requirement to forty units per day, and proved that the patient was sensitive to insulin when the hormone reached its place of action.

No patient should be placed on insulin who has not been instructed that the efficiency of the treatment depends upon proper injection. We give our own patients a small drawing which shows three longitudinal lines on the thighs. Each line has seven marks on it, and the patient is instructed to project these lines on his thighs, and to take his injection day by day into another of the marked spots. Thus, he will return only once every three weeks to the same site (or even later if he uses both legs), and can easily avoid insulin granulations and subsequent poor absorption.

This enumeration of extrapancreatic causes of increased insulin deficiency does not claim to be complete. We have attempted to discuss briefly those mechanisms for which some experimental or clinical evidence can be given. One of the most common clinical

conditions with high insulin requirement will have to be discussed later because its cause is still unknown.

Only short mention should be made of the possibility of specific insulin inhibition by mechanisms other than immunity, and of the question of a specific anti-insulin hormone. In spite of suggestive experimental findings, the existence of these substances is yet too problematic to justify their discussion in a clinical paper.

UNUSUAL INSULIN REQUIREMENTS IN PRACTICE

In the clinic, cases with unusual insulin requirement are relatively rare, but occur frequently enough to present serious problems to every physician who treats diabetes. The condition in which the clinician is most likely to meet this problem is diabetic acidosis and coma. We know little about its development in this diabetic emergency, of all the explanations which have been suggested, a profound disturbance of liver function seems to be the most probable at present. But clinical experience has shown that, here more than in any other state, the early recognition of increased need for insulin will decide the question of success or failure, of life or death. It is one of the great merits of Joslin to have emphasized untiringly that failure in the treatment of coma is often due to too little insulin.

In most other clinical instances, the development of an unusual requirement for insulin follows one or the other of the described pathways, although occasionally it may be spontaneous or idiopathic with no known factor to account for it. The literature contains several excellent clinical summaries,^{1, 12a, b} and a large number of case reports, only the recent ones will be referred to in the bibliography^{11, 12c, 14a-f}. About three thousand units seems to be the largest daily insulin dose ever given.¹⁵ The following is a list of the conditions which have been found most frequently to be associated with a high insulin requirement and which, therefore, can be considered as precipitating factors.

Unusual insulin requirement may be associated with (1) diabetic acidosis and coma, (2) infections and injuries, (3) liver damage (especially cirrhosis and hemochromatosis), (4) endocrine disturbances (acromegaly, hyperthyroidism, adrenal tumors), (5) immunity and allergy, and (6) poor absorption (edema, insulin granuloma). A recent analysis of twenty-six cases from the world literature^{13b} which, however, did not consider all of the above mentioned conditions, gives as precipitating factors five times disturbances of other endocrine

glands, five times hepatic disorder, five times infection, and eight times allergy or immunity. Three cases remained unexplained.

Our enumeration does not claim to be an etiological classification. We are well aware of the fact that, occasionally, one of these complications may leave the diabetes, and the insulin requirement, unchanged. Indeed, clinical experience has shown that, for instance, liver diseases occasionally may increase the insulin sensitivity rather than decrease it, and sometimes diabetic coma may respond well to small doses of insulin.

We do not know the real causes in many instances, and in others we have only an incomplete understanding of their pathways. Yet, in a clinical classification such as the one above, a practical purpose may be served in warning the physician where to expect a sudden rise in insulin requirement. In respect to practical usefulness, this seems to be better than any attempts to classify the unusual insulin requirement according to age, severity or duration. To mention age distribution only, it can be said that extremely high insulin requirements have been found in all age groups, notwithstanding the fact that the juvenile diabetic usually is more sensitive to insulin than the old diabetic. These differences, however, are confined to the normal or physiological limits of insulin requirement.

A few words should be added concerning the problem of immunity and allergy. Occasionally, immunity may be associated with allergic manifestations. Thus, in one of our cases, allergy preceded the development of immunity.¹⁰ In general, however, allergy and immunity are different processes, not only quantitatively but qualitatively. In insulin allergy, even small doses of insulin cannot be tolerated because of the severe reactions of skin and mucous membranes. Yet, insulin may be normally effective in its specific function of lowering the blood sugar. In insulin immunity, even large doses of insulin are tolerated by the organism, but rendered inefficient by antibody inactivation. In a series of eight cases with severe insulin allergy, we found a decreased sensitivity to insulin only three times.¹⁰

DIFFERENTIAL DIAGNOSTIC TESTS

A number of laboratory tests have been described to differentiate the various types of unusual insulin requirement. Some of them are of interest only to the research worker, others so delicate that they can be carried out only in special laboratories.

For practical purposes, the insulin tolerance test, and perhaps

the passive transfer test of Prausnitz-Kuestner, can be used to determine whether localized poor absorption from the skin (poor utilization) or immunological processes are involved in the development of the high insulin requirement. In most other instances, the diagnosis of the precipitating factor is possible clinically without the help of special tests

1 *Insulin tolerance test* 0.1 unit of regular insulin per kilogram of ideal weight is given intravenously. Blood sugar estimations are done prior to injection, and twenty, thirty, forty-five, sixty, ninety, and one hundred and twenty minutes later. A lowering of the blood sugar of 50 mg per 100 cc or more can be considered as normal insulin sensitivity

2 *Passive transfer test* The skin of a normal test person is sensitized by intracutaneous injection of 0.1 cc of the patient's serum. Twenty-four hours later, 0.05 cc of the U-40 crystalline insulin is injected intradermally into the sensitized area, and into a corresponding untreated skin area. The test is read after one-half and one hour, and indicates the presence of antibodies in the patient's blood if redness and swelling have developed in the sensitized area.

THErapy

The aim of all therapeutic procedures is removal of the cause. Recognition of the cause is its prerequisite. In the case of poor absorption, the cause is obvious, and can be eliminated. The proper instruction in the administration of insulin has been discussed above.

In all other instances, the treatment of unusual insulin requirement is the use of even larger doses of insulin. This is true for the treatment of emergency situations as acidosis and infections where, of course, the precipitating or accompanying condition needs its own proper care. It is true also for the treatment of insulin immunity, and for those conditions in which the contributing factors are unknown or not susceptible for specific treatment. There seems to be no limit to the amount of insulin which can be given and tolerated, if the patient is observed carefully, and the physician is prepared for the possibility of sudden hypoglycemic reactions. If large doses of insulin are ineffective, larger doses will bring a response. No case has yet been reported in which a total resistance was observed. Even where, as in some reports of diabetic coma, the blood sugar remained unchanged in spite of large doses of insulin, the accompanying acidosis showed signs of improvement, and even larger doses probably would have been fully successful. In such cases, insulin should be given at

hourly intervals in doses of from 100 to 200 and 300 units, with constant observation of ketonuria, glycosuria and blood sugar. The injections should be decreased in size and spaced at longer time intervals as soon as it becomes apparent from the laboratory tests that an effective level has been reached. Glucose injections to prevent hypoglycemia may become necessary.

In insulin immunity too, the use of larger doses of insulin is recommended. In contradistinction to insulin allergy, where sometimes desensitization with small and frequent intradermal injections have been reported to give results, only exhaustion of the antibody production by more insulin will overcome the insulin deficiency caused by immunity.

SUMMARY

It is shown that the unusual requirement for insulin cannot be due to pancreatic pathology alone, and must have extraneous causes. Some of these processes are discussed, and a clinical classification is given. It is emphasized that, in most instances, the treatment of large insulin requirements is the use of even larger doses.

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RECENT STATISTICS ON DIABETES AND DIABETICS

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I THE DIABETIC POPULATION OF THE UNITED STATES†

Current Prevalence.—The number of persons in the United States with diabetes is not accurately known. The estimates vary widely, running to over a million. It is necessary to make a distinction between the number of known diabetics and the total number with the disease, including cases existing but not yet diagnosed and, therefore, unidentified. Some of the confusion regarding estimates of diabetics arises from the failure to state whether the figure includes an allowance for unidentified cases. There are large numbers of such cases, mostly mild diabetics, among persons in late middle life and old age. Indeed, the findings of Selective Service examinations^{2, 3} indicate that unidentified cases in early adult life may be much more numerous than was suspected hitherto.

The best available data, based upon past surveys, would indicate the number of *known* cases to be in the neighborhood of 700,000. This estimate is derived from the National Health Survey⁴ made in the winter of 1935-1936 under the auspices of the U. S. Public Health Service. This is the most extensive as well as the latest survey of chronic disease in the United States. It covered approximately 2,500,000 persons living in 700,000 households in eighty-three cities and was planned so as to constitute a representative sample of the general urban population of the country. The prevalence rates of diabetes by age and sex as found in this survey are shown in Table 1.

The number of diabetics in the United States in 1937, computed on the basis of these age-specific prevalence rates, was 450,000 but the statisticians of the Public Health Service made certain adjustments of the figures and published an estimate of 660,000 as of that year.⁵ Applying the prevalence rates by sex and age to the estimated population of the United States for 1946 yields a current figure of 575,000. This figure is probably an underestimate of the total in the United States but the amount of upward adjustment to be made in

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† Details regarding the methods of statistical analysis and sources of data for this section of the article will be found in Reference 1.

the figure is rather conjectural. For reasons stated elsewhere,¹ the upward adjustment made by the Public Health Service of the National Health Survey figures was much too generous. That some upward adjustment is required, however, is clear from the fact that with the increasing duration of life of diabetics, there is an increasing excess of new cases over deaths and this itself would tend to raise the age-specific figures shown in Table 1. It is likely also that, in a study like the National Health Survey, appreciable numbers would escape enumeration. Altogether, an upward adjustment of 25 per cent would be a generous allowance for these two factors. Although studies^{6, 7} have been made of the understatement of diabetes in mortality reports, the results of such studies are not directly applicable to prevalence estimates based upon surveys.

TABLE 1

NUMBER OF DIABETICS AND PREVALENCE RATES PER 1000 BY SEX AND AGE,
NATIONAL HEALTH SURVEY, 1935-1936

Age	Prevalence Rate per 1000			Number of Diabetics in Survey		
	Total	Males	Females	Total	Males	Females
All ages	3.67	2.73	4.53	9182	3285	5897
Under 15	0.38	0.35	0.41	229	105	124
15-24	0.59	0.62	0.57	265	129	136
25-34	1.00	0.90	1.08	425	178	247
35-44	2.61	2.01	3.16	1031	385	646
45-54	6.56	4.49	8.64	1989	680	1309
55-64	14.25	9.96	18.20	2604	873	1731
65-74	19.87	15.14	23.80	2030	702	1328
75-84	15.86	14.07	17.23	553	212	341
85 and over	6.69	6.40	6.88	36	14	22
Unknown				20	7	13

Annual Number of New Cases.—New cases of diabetes are currently estimated to number at least 55,000 annually. This estimate is based upon the data of the National Health Survey, together with mortality data among diabetic patients. For the latter, the experience of the George F. Baker Clinic during 1926 to 1929 was used.⁸ By suitable actuarial technic, it is possible to estimate, from these data, the annual onset rates for diabetes by sex and age and, by applying these rates to the population, the number of persons becoming diabetic during the course of a year. The age-specific rates are shown in Figure 51.

This figure of 55,000 applies again to known diabetics. It is, there-

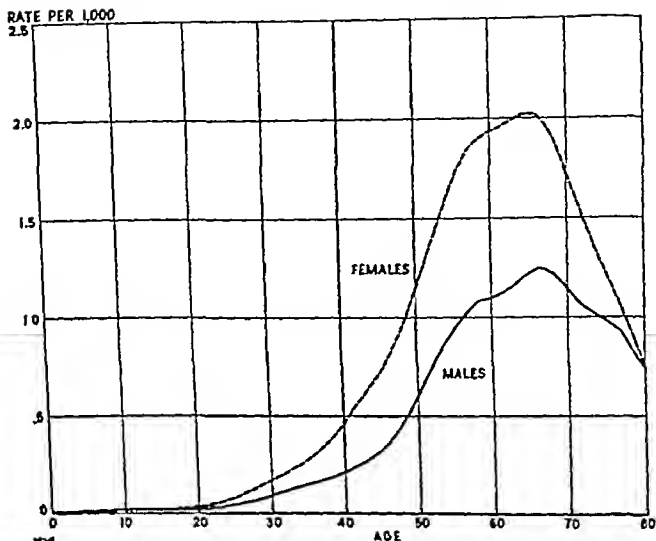


Fig 51 -Diabetes onset rates per 1000 (Chances of becoming diabetic within the year of age) United States 1935-1936

TABLE 2

CHANCES PER 1000 OF EVENTUALLY BECOMING DIABETIC, BY SEX AND AGE, UNITED STATES 1935-1936

Age	Males	Females
Under 10	22.1	41.5
15-19	22.4	42.0
20-24	23.6	42.3
25-29	23.8	42.6
30-34	23.8	42.6
35-39	23.7	42.2
40-44	23.4	41.3
45-49	21.9	39.4
50-54	20.7	36.3
55-59	18.1	30.7
60-64	16.8	23.8
65-69	11.3	16.6
70-74	7.7	10.0
75-79	4.6	5.2
80-84	2.0	2.0
85-89	0.4	0.4

fore, a minimum and is subject to upward adjustment to allow for unidentified new cases of the disease. Moreover, this figure is not static. It fluctuates in accordance with the influence of the several factors that cause variation in the onset rate of the disease from year to year as well as with changes in composition of the population.

Potential Diabetics.—Using the annual onset rates according to age and sex, and the life tables for the white population of the United States for 1935, a computation was made of chances of eventually becoming diabetic, with the results shown in Table 2. Changes in mortality since 1935 would not alter these figures materially. When, therefore, the probabilities for each sex-age group are applied to the 1946 population of the United States, it is found that about 4,125,000 persons or 2.9 per cent of this population will eventually become diabetic. For males in the population, this percentage is 2.1 per cent, for females, it is 3.8 per cent, or almost double the proportion of males.

II DEATH RATES FROM DIABETES

General Considerations.—(a) *Classification of Diabetes for Mortality Statistics*—Population statistics on diabetes mortality are based on those deaths in which the disease is reported as the sole cause or is selected as the primary cause. When two or more causes of death appear on the death certificate, registration offices follow a systematic procedure of designating which is to be taken as primary. Thus, in this country, if both cancer and diabetes are jointly certified, cancer is assigned as the cause of death. The chief diseases or conditions which are thus ranked ahead of diabetes are cancer, all forms of violence, tuberculosis and most other infectious diseases, and most diseases of the puerperal state.⁹ Occasionally when the circumstances are fully stated these rules are modified. Not all countries follow American joint-cause practice. In some, the judgment of the certifying physician is accepted as to which cause is primary.

Regardless of what procedure is followed, the number of deaths from diabetes is affected by the decision of individual physicians whether or not to mention diabetes on the death certificate if, in their judgment, the diabetes was well controlled and death resulted from some intercurrent condition. While the opinion has been expressed that physicians frequently do not mention diabetes in such circumstances, there is not sufficient basis to judge if this practice is increasingly followed.

At intervals, the Census Bureau has made tabulations of the chief contributory causes in relation to primary causes of death. In 1940,

the last occasion on which this was done, diabetes was the sole or primary cause in 35,015 deaths and the number in which it was the chief contributory cause was an additional 3991 deaths^{10 11} The total number of deaths in which diabetes was mentioned on the death certificate was thus 11 per cent greater than the number of deaths from diabetes.

(b) *Crude versus Standardized or Age-Adjusted Rates**.—The most commonly used measure in comparing mortality statistics is the annual crude death rate, which is simply the number of deaths within a year divided by the mean population for the year. For all causes of death, this ratio is usually expressed per 1000 population, for specific causes, usually per 100,000 population. The crude death rate, computed as indicated, is influenced strongly by the prevailing distribution of the population according to age and sex. For a condition such as diabetes, where mortality increases rapidly from infancy to old age, the crude death rate for a community with a large population of aged persons will be high, as compared with another community with a large concentration of young people. A similar situation arises where mortality for the two sexes is different.

As a gross measure, the crude rates have valid uses. However, if the interest lies in ascertaining whether there is an intrinsic improvement or deterioration in the situation from year to year for a particular area or whether there are essential differences in mortality between areas, it is necessary either to compare death rates computed specifically for each sex and age, or as a convenient though not altogether satisfactory alternative, to use so-called age-adjusted or standardized rates. The standardized death rate is usually computed by multiplying the number of persons in each age group of a particular population which is taken as the standard by the observed death rate in the corresponding age group of the population under study, each product represents "expected" deaths in an age group of the "standard" population. The sum of these "expected" deaths, divided by the total number of persons in the "standard" population, gives the standardized or age-adjusted rate. (Essentially, this type of standardized rate is no more than a weighted average of the age-specific death rates in which the constants are the numbers in each age group of the "standard" population.) Further refinements are possible to allow for variations in the proportions of males and females or in the proportions of white and colored persons in the observed population. The results vary according to the standard used so that it is not correct to

* A comprehensive discussion of this subject will be found in Reference 12.

compare directly adjusted death rates computed by different standards. Consequently, some thought must be given as to the suitability of the standard to be used.

A commonly used standard is the Standard Million of Population of England and Wales, 1901. The adjusted death rates published for the industrial mortality experience of the Metropolitan Life Insurance Company, including the figures on diabetes which will be quoted later, are generally based on this standard. Recent studies¹⁸ of vital statistics by the U. S. Census Bureau have made use of the age distribution of the country's population enumerated in 1940 as the standard in computing age-adjusted death rates. Federal or state figures on diabetes cited in this paper are based on this second standard.

(c) *Relationship between Insulin and the Death Rates from Diabetes in the General Population*—Physicians as well as laymen have looked to the facts on diabetes mortality trends in the general population to show the effect of insulin and other advances in the treatment of diabetes on the improvement in the lot of diabetics. For a very brief period after the discovery of insulin, they were not disappointed but afterwards were disconcerted by the subsequent increase in the diabetes death rate. Actually, except in a very limited way, death rates in the general population cannot serve as a measure of the improvement in diabetes treatment because the trend of the death rate from diabetes in the general population is influenced by many variables which are not directly related to the actual mortality recorded among diabetics. Most important is the changing size and composition of the diabetic population which is affected by the trend in the sex and age composition of the population, by the rate of onset of new cases of diabetes, by the rate of discovery of cases and, since diabetes is not curable, by the mortality among diabetics. Adjustment for changes in the age and sex composition of the population eliminates wholly or largely only one of these variables. There is no statistical basis for measuring the effect of the other variables. We know that the rate of discovery of diabetes has risen because of the increased use of urine and blood sugar tests. Overnutrition relative to bodily needs, so characteristic of our increasingly mechanized civilization, may have brought a true increase in the disease. Incidentally, a common fallacy in interpreting the increase in diabetes death rates at the older ages has been to ascribe this entirely to postponement of diabetes deaths. Only a small part of this upward trend can be thus explained.

The only true measure of the improvement in the lot of diabetics

is to observe the trend of mortality in a "diabetic population." This involves a knowledge of what happens in a particular group of diabetic patients carefully followed up over a period of years. Fortunately, this has been done consistently at the George F Baker Clinic, and life tables covering a considerable span both of the preinsulin and postinsulin years are available for that experience.

TABLE 3

DEATH RATES PER 100,000 FROM DIABETES MELLITUS
IN VARIOUS COUNTRIES OF THE WORLD 1938

Country	Death Rate
United States	23.9
Canada	13.8
Argentina	7.0 ^b
Uruguay	5.8 ^a
Chile	4.6 ^a
England and Wales	11.5
Scotland	17.2
Northern Ireland	12.9
Irish Free State	9.2
Norway	9.0
Sweden	10.8
Denmark	20.4
Finland	8.1
Germany	19.3 ^b
Austria	12.2 ^a
Switzerland	15.4 ^b
Netherlands	14.5
Belgium	19.7 ^a
France	10.1 ^b
Italy	10.5
Spain	9.4 ^a
Portugal	6.2 ^a
Lithuania	3.7 ^a
Estonia	3.0 ^b
Czechoslovakia	12.3 ^a
Hungary	6.1 ^a
Bulgaria	7.0 ^a
Romania	3.0 ^b
Greece	4.9
Australia	17.7
New Zealand	10.8
Union of South Africa	13.5
Japan	4.2
^a 1937 ^b 1936 ^c 1935 ^d 1934	

International Data—Because of the war, recent statistics on diabetes mortality are available for only a few countries. Consequently, international comparisons must be based on prewar data. Table 3 shows the latest prewar death rates from diabetes in various countries of the world. Some degree of caution is necessary in interpreting the figures because there is some variation from country to country, in the

reporting of causes of death by physicians and in the classification by vital statistics offices of the primary cause of death when more than one is stated. Despite this, it is clear that the range of mortality from diabetes as reported throughout the world is quite wide. The death rate in the United States is the highest recorded anywhere. The rates are relatively high in most of western Europe and in the white population of countries in the British Commonwealth. Low rates are found quite uniformly in the predominantly agricultural countries of eastern and southern Europe and in Latin America. As for the Far East, the only figures available relate to Japan in which the rate also is very low. This is in conformity with clinical reports which indicate a low prevalence of diabetes in this area.

While many factors enter into these international differences in diabetes rates, it should be noted that many countries with low rates have relatively younger populations. If correction is made for this age factor, a part of the difference in rates is eliminated. This factor is important in comparing diabetes death rates for the United States and Canada.

Geographical and Racial Variations within the United States.—Crude and adjusted death rates from diabetes in each state, arranged according to geographic divisions, are shown in Table 4. It is readily seen that the highest age-adjusted rates are found in the urbanized industrial states in the northeastern section of the country, and the lowest rates in the southern and southwestern states. The effect of differences between the states with respect to age distribution of the population is shown by comparing the crude and age-adjusted rates. The range from minimum to maximum for the latter is appreciably smaller than for the crude rates. The effect of correcting for age differences is particularly evident in comparing the diabetes death rates of the white and non-white population. The crude rate for the non-white is almost one third less than for the white population, but the adjusted rate shows a difference of only 13 per cent.

It is notable that the age-adjusted rates for the non-white population which, for most states relate to Negroes, are generally as high as or higher than the rates for the white population. It is clear, then, that the higher rate among white persons for the country as a whole represents largely the difference between the two populations with respect to geographical distribution. It is generally true that in states where the Negro population is urbanized and has access to abundant medical and health services, the diabetes death rates in non-white populations are high.

TABLE 4

CRUDE AND AGE-ADJUSTED* DEATH RATES PER 100 000 FROM DIABETES MELLITUS IN THE UNITED STATES AND EACH STATE, BY PLACE OF OCCURRENCE, WHITES AND NON WHITES SEPARATELY 1940

Geographic Division—State	Total		White		Non-White	
	Adjusted	Crude	Adjusted	Crude	Adjusted	Crude
United States	26.6	26.6	26.7	27.6	23.2	17.9
New England						
Maine	25.3	32.1	25.3	32.1	†	†
New Hampshire	28.1	37.0	28.1	37.1	0	0
Vermont	27.0	33.7	27.0	33.7	0	0
Massachusetts	29.8	35.7	29.8	35.8	30.1	25.6
Rhode Island	35.4	33.8	35.0	38.5	†	†
Connecticut	32.8	35.8	32.6	35.9	40.8	22.5
Middle Atlantic						
New York	39.0	40.6	38.8	41.2	32.7	17.9
New Jersey	35.6	36.4	31.9	36.2	31.0	17.9
Pennsylvania	35.9	36.3	33.4	36.3	46.5	26.3
East North Central						
Ohio	28.1	31.3	27.6	31.2	32.8	17.4
Indiana	24.2	28.1	23.8	27.9	35.7	17.5
Illinois	32.0	31.1	31.5	31.1	22.4	17.5
Michigan	27.9	26.7	27.7	26.8	21.9	17.4
Wisconsin	26.0	28.4	25.9	28.4	†	†
West North Central						
Minnesota	24.5	26.8	24.4	26.8	†	†
Iowa	23.1	28.4	23.9	28.8	†	†
Missouri	21.6	25.3	21.4	25.3	†	†
North Dakota	28.7	26.6	28.7	26.6	†	†
South Dakota	23.0	23.2	23.2	23.2	†	†
Nebraska	24.7	28.1	24.8	28.1	†	†
Kansas	21.7	26.0	21.8	26.0	†	†
South Atlantic						
Delaware	27.6	30.0	27.6	30.0	†	†
Maryland	31.5	31.2	31.5	31.2	†	†
District of Columbia	31.9	33.5	31.9	33.5	†	†
Virginia	23.5	20.1	23.5	20.1	†	†
West Virginia	21.6	17.4	21.6	17.4	†	†
North Carolina	20.0	14.2	20.0	14.2	†	†
South Carolina	18.7	12.6	18.7	12.6	†	†
Georgia	15.3	12.2	15.3	12.2	†	†
Florida	20.1	19.6	19.5	19.6	†	†
East South Central						
Kentucky	16.9	15.4	16.9	15.4	†	†
Tennessee	16.4	14.4	16.4	14.4	†	†
Alabama	15.9	12.2	15.9	12.2	†	†
Mississippi	16.9	13.4	16.9	13.4	†	†
West South Central						
Arkansas	17.4	10.5	17.4	10.5	†	†
Louisiana	22.4	11.2	22.4	11.2	†	†
Oklahoma	16.0	11.4	16.0	11.4	†	†
Texas	17.2	10.6	17.2	10.6	†	†
Mountain						
Montana	19.2	15.2	19.2	15.2	†	†
Idaho	19.6	11.2	19.6	11.2	†	†
Wyoming	20.1	11.2	20.1	11.2	†	†
Colorado	16.4	11.2	16.4	11.2	†	†
New Mexico	11.1	11.2	11.1	11.2	†	†
Arizona	11.1	11.2	11.1	11.2	†	†
Utah	11.1	11.2	11.1	11.2	†	†
Nevada	11.1	11.2	11.1	11.2	†	†
Pacific						
Washington	11.1	11.2	11.1	11.2	†	†
Oregon	11.1	11.2	11.1	11.2	†	†
California	11.1	11.2	11.1	11.2	†	†

*Adjusted on basis of age distribution of 1940. †Less than 10 deaths.

Urban-Rural Differences in the United States.—For the country as a whole, the age-adjusted death rate from diabetes is higher in the cities than in rural areas. As Table 5 shows, the urban rate among white and colored persons combined is more than 50 per cent above the rural rate. The differential is even larger, more than 100 per cent, for the non-white population. A goodly part of these differences is accounted for on a purely geographical basis. A large proportion of the rural population lives in the south and southwest where diabetes death rates are generally low. Conversely, the concentration of urban population is in the north where diabetes rates are highest. Intra-regional or intrastate comparisons of urban and rural rates generally show smaller differentials.

TABLE 5

AGE-ADJUSTED* DEATH RATES PER 100,000 FROM DIABETES BY POPULATION SIZE GROUP, BY RACE AND SEX AND BY PLACE OF RESIDENCE, UNITED STATES, 1940

Population Group	Total			White			Non-White		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
United States—Total	26.6	20.2	33.0	26.7	20.6	32.9	23.2	14.9	32.1
Urban—Total	31.6	24.3	38.2	31.4	24.5	37.5	31.5	19.5	43.3
Places of 100,000 or more population	33.8	25.4	41.6	33.7	25.6	41.0	32.3	20.2	41.5
10,000 — 100,000 population	29.8	22.8	36.0	29.5	23.0	35.3	31.9	18.7	41.1
2,500 — 10,000 population	28.2	24.0	32.0	28.1	24.3	31.7	27.8	19.5	35.8
Rural	19.8	15.4	24.9	20.2	15.8	25.3	14.9	10.9	19.6

* Adjusted on basis of age distribution of the total population of the United States enumerated in 1940

There is relatively little correlation between size of city and the diabetes death rate except among white females. In each population-size group, the diabetes death rate of white males is higher than that for the colored, whereas, among females, the reverse is true except in rural areas.

Trend of Diabetes Mortality in the United States.—Statistics on the trend of crude and age-adjusted death rates from diabetes are shown in Table 6 for the United States and for Industrial policyholders of the Metropolitan Life Insurance Company and the age-adjusted rates for the insured group are shown in Figure 52. For various reasons it is impossible to get an accurate picture of the long-term trend in mortality from the disease in the general population of the United States. It was not until 1933 that figures became available for the entire country. Prior to that date, fluctuations in the rate

reflect in part the effect of the admission of additional states to the Expanding Death Registration Area, for as we have seen, there is considerable variation in diabetes mortality from state to state. There was some distortion of the rates during the war years due to the

TABLE 6

CRUDE AND AGE-ADJUSTED DEATH RATES PER 100 000 FROM DIABETES MELLITUS IN THE GENERAL POPULATION OF THE UNITED STATES AND AMONG INDUSTRIAL POLICYHOLDERS OF THE METROPOLITAN LIFE INSURANCE COMPANY, 1900-1945

Year	United States*		Metropolitan Life Insurance Co	
	Adjusted†	Crude	Adjusted‡	Crude
1945	‡	26.6	16.2	24.8
1944	24.4	26.4	18.6	27.4
1943	25.8	27.1	19.9	28.1
1942	21.6	25.4	19.8	27.8
1941	25.0	25.4	19.3	26.3
1940	26.6	26.6	22.1	29.5
1939	26.0	25.5	21.4	27.4
1938	21.8	23.9	19.7	24.2
1937	25.0	23.7	21.0	25.4
1936	23.5	23.7	20.6	24.7
1935	24.3	23.3	20.5	24.4
1934	21.6	22.2	20.7	24.2
1933	21.1	21.4	20.8	24.0
1932	21.9	22.0	20.7	23.0
1931	23.5	20.4	19.9	21.1
1930	22.2	19.1	18.3	18.4
1925	20.7	16.8	16.8	15.2
1922	13.4	18.3	18.3	16.7
1920	19.8	16.1	15.6	13.6
1915	21.5	17.6	16.6	14.5
1910	18.9	15.3	15.1‡	13.1‡
1905	17.0	14.1	‡	‡
1900	13.0	11.0	‡	‡

* Expanding Registration Area 1900 to 1932. Total U.S. 1933-1945 Death rates for the war years based upon population excluding the Armed Forces overseas.

† Adjusted on basis of age distribution of the total population of the United States enumerated in 1910.

‡ Adjusted on basis of age distribution in Standard Million of Population of England and Wales, 1901.

§ Not available.

‡ 1911.

exclusion of persons in military service overseas, obviously a medically select group. These limitations do not apply to the large segment of the population comprised by the industrial policyholders of the Metropolitan Life Insurance Company. The composition of this population is known within close limits year by year. The statistics

were not greatly disturbed by wartime population changes since the insurance in force at the time of our entry into the war was largely unaffected and, consequently, the experience includes insured policyholders in military service. Although the insured group is drawn predominantly from the urban industrial population, there is a high correlation between this group and the general population in regard to mortality trends.

The crude death rate from diabetes in the United States rose with few interruptions from 21.4 per 100,000 in 1933 to a peak of 27.1 in

AGE-ADJUSTED DEATH RATES PER 100,000 FROM DIABETES MELLITUS

Metropolitan Life Insurance Company, Industrial Policyholders, 1911-1945, Ages 1 to 74

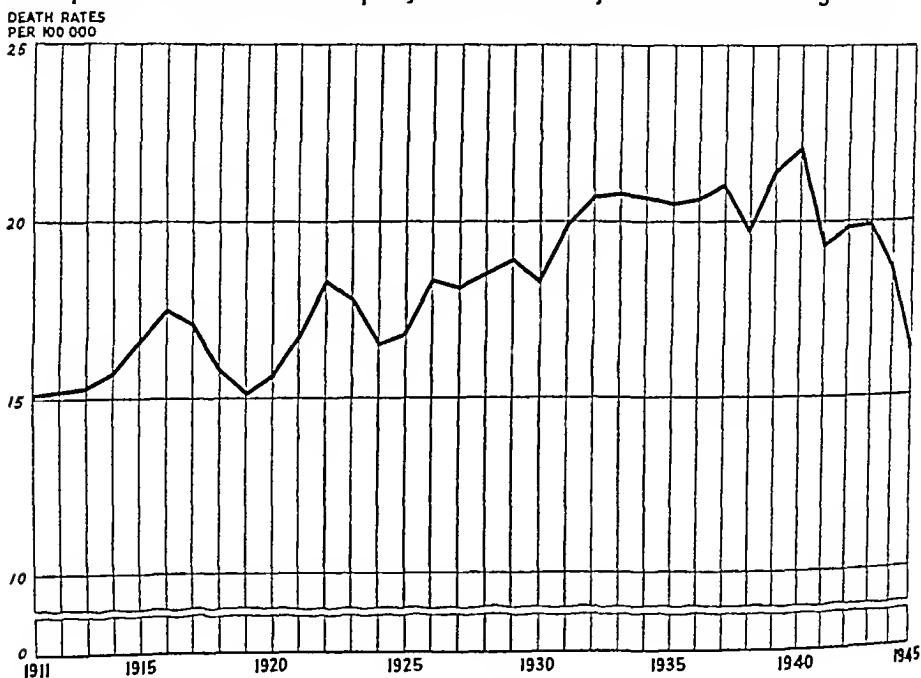


Fig 52

1943, an increase of 27 per cent. The age-adjusted rate, however, was much more stable. The rise from 1933 to the maximum in 1940 was only 10 per cent. The adjusted rate subsequently declined, the figure for 1944 being only 1 per cent higher than in 1933 as against an increase of 23 per cent in the crude rate. If, moreover, consideration is given to the effect of excluding persons in military service abroad, the adjusted rate for 1944 was probably actually lower than that for 1933.

The Metropolitan experience, which is available for the period

since 1911, shows a steady increase in the crude death rates from diabetes to a maximum in 1940. Since then, the rate has fallen rather rapidly, with the 1945 rate the lowest since 1938. This population, too, has had a considerable increase in the proportion of older persons, and when allowance is made for this, the age-adjusted rates show a very small rise after 1930. The maximum rate, recorded in 1940, was only 11 per cent above that for 1931. Since 1940, the age-adjusted rate has dropped sharply, and by 1945, the rate was at the lowest level since 1920.

As indicated earlier, a great part of the long-term increase in age adjusted death rates from diabetes reflects the more frequent discovery of the disease as a result of the development of relatively simple and inexpensive methods of urine and blood tests for sugar, the wider use of these tests in clinical practice and in industrial and

TABLE 7
DEATH RATES PER 100 000 FROM DIABETES MELLITUS,
ENGLAND AND WALES, 1935-1945

Year	Death Rate
1945	9.4
1944	9.6
1943	10.2
1942	10.6
1941	11.7
1940	12.8
1939	12.4
1938	11.5
1937	12.4
1936	12.5
1935	11.3

insurance medicine, and the vastly increased interest in diabetes following the discovery of insulin. Short term fluctuations in diabetes, as in chronic diseases generally, reflect variations in the prevalence of such infectious diseases as pneumonia. The importance of this factor naturally has been greatly reduced in recent years, more or less in proportion to the effectiveness of new chemotherapeutic methods in combating infections.

A notable feature of the trend in diabetes mortality is the decline recorded during the recent war years. The experience of England, shown in Table 7, is even better than ours. At the low point in 1945 the English death rate from diabetes was more than 25 per cent under the peak of 1940 and more than 20 per cent under the average for 1935-1935. Unfortunately data are not available for other European belligerents during the recent conflict but during the first World War a decline in the death rate from diabetes was observed in Eng-

land and Germany. It would appear that a significant part of the reduction in diabetes mortality recorded in the two wars is genuine and that restrictions on food supply are a factor in this trend. The enforced reduction in food intake tends to ameliorate the condition of many diabetics and also helps to prevent or postpone the onset of the disease in susceptible individuals. In this country at least, the favorable trend in diabetes during World War II reflects also the absence of serious respiratory epidemics during the entire war period, as well as the success of chemotherapy. This has proved a boon to diabetics not only in combating pneumonia and other infections but also in the successful management of surgical complications of diabetes. On the other hand, the decline in the diabetes death rate is spurious to some extent in that, with the wartime disruption of medical practices, the reporting of causes of death probably suffered in quality.

Trends by Sex and Age.—Figure 53 is a chart showing, on a semi-logarithmic scale, the trends of the diabetes death rates among white male and white female industrial policyholders of the Metropolitan Life Insurance Company from 1911 to 1945, at all ages 1 to 74 years, and for separate age groups. At all ages combined, there is a sharp divergence between the trend of the age-adjusted rates for males and females. The rates among males have fluctuated within a rather narrow range up to comparatively recent years when they fell sharply, whereas the rates for females have climbed rather steadily, again except in recent years.

In both sexes, the death rates among children and young adults fell sharply after insulin was discovered, and eventually established extremely low levels which have been maintained with relatively small fluctuations for several years. Among males, the post-insulin downward trend extends to age 55, and only after age 65 has there been any long-term increase in the death rate from the disease. Among females, however, a long-term increase after insulin is evident in every age group past 45.

The most notable feature of the wartime mortality experience for diabetes is the considerable decline in the death rates in late middle life and old age. The rates in 1944 and 1945 were the lowest in years. However, the recent improvement at the older ages was sufficient to wipe out only a fraction of the long-term increase in the death rates from the disease. Consequently, at ages 65 to 74, the rate in 1941–1945 among males was 34 per cent higher than in the preinsulin years 1920–1922, and among females, it was 81 per cent higher than in 1920–1922.

DEATH RATES PER 100,000 FROM DIABETES MELLITUS BY SEX AND AGE

Metropolitan Life Insurance Company White Industrial Policyholders 1911-1945



Fig. 51.

III LONGEVITY OF DIABETICS

As indicated earlier, the best measure of the improvement in diabetes is the mortality experience among diabetic patients. Data are available on the extensive experience of the George F. Baker Clinic in Boston up through 1938. Table 8 shows the huge reductions in the death rate of diabetic patients at various ages, particularly since insulin came into use, and the correspondingly large increases in the expectation of life of diabetics. There has been a progressive increase in longevity right through the insulin period, and it has been especially large at the childhood ages.

TABLE 8

DEATH RATES PER 1000 AND EXPECTATION OF LIFE AT SPECIFIED AGES AMONG DIABETIC PATIENTS IN SUCCESSIVE PERIODS, 1897-1938. EXPERIENCE OF GEORGE F. BAKER CLINIC, BOSTON, MASSACHUSETTS

Age	Death Rates per 1000					Expectation of Life				
	Naunyn Era 1897-1914	Allen Era 1914-1922	Insulin Era			Naunyn Era 1897-1914	Allen Era 1914-1922	Insulin Era		
			1922-1926	1926-1929	1929-1938			1922-1926	1926-1929	1929-1938
10	824.0	386.1	61.4	19.1	8.1	1.3	2.6	14.3	31.7	39.8
15	623.0	398.8	84.0	14.9	9.2	1.7	2.8	14.1	29.3	36.2
20	614.0	410.8	89.4	18.3	12.6	1.8	3.2	15.0	26.4	33.1
25	585.6	342.8	77.4	28.0	15.9	2.1	4.0	15.9	24.1	30.3
30	359.8	236.8	74.8	33.4	13.9	4.1	6.3	16.8	22.7	27.6
35	200.6	152.1	57.5	28.5	10.6	6.2	8.8	18.0	21.3	24.2
40	165.7	115.1	34.7	23.8	16.6	7.7	10.0	17.2	18.9	20.6
45	119.8	87.1	33.4	26.3	22.2	8.5	10.5	14.8	16.0	17.4
50	96.1	77.4	45.3	41.0	30.6	8.0	9.5	12.3	13.2	14.4
55	97.1	90.1	64.2	56.5	46.4	6.4	8.2	10.2	11.2	11.8
60	88.8	112.5	85.2	70.1	66.6	4.6	6.6	8.6	9.3	9.8

Figures of average duration of life since onset in fatal cases, records of which are available up to May 15, 1946, show significantly large increases in practically every age group. The median duration of life in fatal cases reported since January 1944 was fourteen years as compared with only ten years for patients dying between 1930 and 1935. This increase in duration of life in fatal cases is not an exact measure of the increase in longevity of diabetics but is a satisfactory index of its trend.

SUMMARY

1. Estimates for the United States of the prevalence of diabetes, the annual rate of onset of the disease, and chances of eventually becoming diabetic are presented. Known diabetics are estimated to number

about 700,000 in 1946, and the annual number of new cases is at least 55,000. It is also estimated that 21 per cent of the males and 38 per cent of the females in our present population will eventually become diabetic.

2. Fundamental considerations in the use and interpretation of mortality statistics on diabetes are discussed.

3. Statistics are presented on death rates from diabetes in various countries of the world, and on variations by state, racial group and size of the community for the United States. It is found that the death rate in this country is the highest in the world, that within the country, the rates are highest in the north and lowest in the south and southwest, and that in most states, the rate in the white population is lower than in the non white population.

4. The long term trend of diabetes mortality in this country has been upward, even after allowance is made for the aging of the population. The increase has been greatest among older women. In the recent war years, however, the trend was reversed. The reasons for the long and short term variations in the trends are discussed.

5. The effect of advances in the treatment of diabetes is best measured by the mortality experience in a diabetic population. Such an analysis, based upon the experience of the George F. Baker Clinic, shows a reduction in the death rates among diabetic patients. The improvement has been spectacular for young diabetics since insulin came into use.

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INCENTIVES TO THE TREATMENT OF DIABETES MELLITUS

F D W LUKENS, M D *

THE aim of this presentation is to outline the influence of treatment on the course of diabetes. In doing this, selected examples rather than thorough reviews will be used to indicate the facts which encourage the early and sustained control of this disease. Differences of opinion exist and further information is needed on many of the aspects of diabetes which are but briefly assembled here.

TREATMENT OF EARLY DIABETES

If treatment is to be started promptly there must be no improper temporizing about the diagnosis. All glycosuria or hyperglycemia is diabetes until proved otherwise. The diagnosis of diabetes ought to be established within a few days after the first laboratory or clinical information suggesting its presence. Treatment ought to be started at once in the obvious case or after no more than a few days of appropriate study in the doubtful case.

The first object of treatment is to bring about as much improvement as possible in the diabetes. Remissions of diabetes can occur as shown by recent reports^{1, 2, 3, 4}. Note that the word "remission" and not "cure" is used. A remission means that the diagnosis of diabetes has been made and that the disease has so improved that without insulin treatment the blood sugar stays at a normal level on a diet sufficient to maintain normal weight and strength. The majority of such patients will still have an impaired glucose tolerance and diabetes will usually become manifest during an infection. Remissions must thus be distinguished from the normal state in which the tolerance test is normal and carbohydrate metabolism is not grossly disturbed by infection. In spite of these limitations the attempt to maintain the greatest possible insulin reserve and to retard the progress of the disease appears logical.

The incidence of remission is little more than a guess. Joslin⁵ mentions fourteen cases of "possibly arrested" diabetes in 1000 juvenile diabetics (1.4 per cent). In a series of 517 patients Lukens and Dohan

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found nine or 17 per cent in whom remissions had occurred. These figures raise two questions How much effort is being made to bring about such improvement? Could these figures be bettered if all early diabetics were treated more intensively? Remissions have occurred predominantly in patients treated early in the disease To the nine cases of uncomplicated remission² were added six cases of diabetes showing marked improvement after recovery from infection and four cases of mild diabetes managed by dietary treatment alone This made a series of nineteen cases in which marked improvement occurred Seventeen of these nineteen patients were treated within the first four months of the recognition of the disease The mechanism of

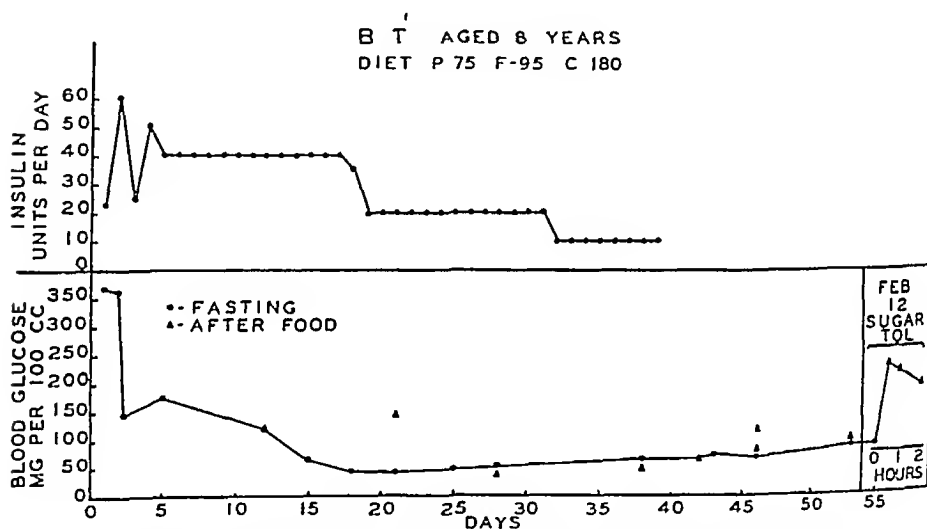


Fig 54—The response to treatment in a patient with early diabetes

this improvement in man is not understood but in experimental diabetes early treatment has resulted in anatomical recovery of the early lesions of the islets⁵

Juvenile Diabetes.—In the case of juvenile diabetics, Jackson, Boyd and Smith³ and, more recently, Brush⁴ have emphasized the value of early care For example, Brush⁴ reported thirty-nine children treated early and intensively Within six weeks all but four of them so improved that they required only 10 units of insulin or less In all but one of his patients the duration of diabetes was less than four months when treatment was begun Brush notes the less favorable response when aggressive treatment is delayed and remarks, "The golden opportunity for bringing about maximal functional recovery may present itself only once" In children, it seems clear that some improve-

ment of diabetes is possible by appropriate treatment and Figure 54 illustrates the type of response which has been described. This boy had been found to have diabetes a month before his admission in acidosis. After the prompt control of his diabetes the insulin was not reduced at once but a slow gradual reduction was made over a period of six weeks. Although he had several blood sugars in the fifties he never had reactions. When insulin was stopped his blood sugar remained normal on a diet adequate for his age. However, the sugar tolerance test was still diabetic. A few weeks after discharge he required 10 units of protamino insulin. One would expect this from the tolerance test and from the knowledge that he must meet the metabolic demands of growth. This course of events would also be expected from our knowledge of the hereditary factor in diabetes.

There is a hereditary element in diabetes, as Joslin and Whitto¹ have shown. In 1942 Woodyatt and Spetz² demonstrated the phenomenon of anticipation in diabetes. This means that the disease tends to appear at an earlier age in each succeeding generation of the diabetic family. This observation has recently been related to a simple anatomical characteristic, namely, the gross pancreatic weight.³ The weight of the pancreas in diabetics of all ages has not been distinctly different from the normal. Young diabetics, however, differed strikingly from the normal. Of nineteen adult diabetics less than 30 years of age fifteen had pancreatic weights less than 60 gm, the minimum normal weight according to Warren.⁴ Of thirteen nondiabetics only one had a pancreas weighing less than 60 gm. In this age group 79 per cent of diabetics and only 8 per cent of normals had a small pancreas. If this ratio is maintained in a larger series of cases it may explain why improvement is inevitably limited in juvenile diabetes. This does not mean that the possible benefits of treatment should be neglected. Both the possibility of improvement and its limitations have been mentioned in order that the best care may be intelligently pursued.

Diabetes in Adults—In adults it is likewise possible to secure improvement in patients treated well from the first. Among adults there are some particularly capable of improvement. They are the obese diabetics. Table 1 gives examples of the success and failure to secure remissions. Improvement is relatively frequent in association with reduction in weight and it is occasionally encountered without weight loss. Most obese adult diabetics can be benefited by weight reduction regardless of the duration of their diabetes. In our series of nineteen cases⁵ the duration of remission ranged from one month to ten years.

When these patients were last seen ten remissions were maintained and nine had relapsed. Only one relapse was unexplained. The other eight were due to gross neglect of diet. The obvious comment about the cases which failed to respond is that the onset of diabetes is difficult to determine in adults and the disease may have been of longer duration than the symptoms.

TABLE 1

RESULTS OF INTENSIVE TREATMENT OF DIABETES WITHIN THREE MONTHS OF ONSET OF SYMPTOMS

Patient	Body Weight Deviation from Average Normal, Per Cent	Blood Glucose, Mg per 100 Ml		Insulin, Units per Day
		Fasting	1 Hr after Glucose	

Cooperative patients showing improvement

H H	1a	+23	287	483	85
	2a	+28	95	153	None
M Z	1	+25	221	383	30
	2	+6	94	212	None
G T	1	+17	228	375	10
	2	-1	103	135	None

Cooperative patients not showing improvement

P P	1	-2	180	252	None
	2	0	—	180b	30
P S	1	0	232	—	19
	2	+7	—	173	20
I B	1	0	194	373	23
	2	-3	—	397	29

a, 1 = Observation before treatment, 2 = after treatment.

b, Highest value after insulin and breakfast.

A comment on the meaning of obesity in diabetes may be made at this point. In carefully conducted studies Newburgh⁹ has described the diabetic sugar tolerance test of the obese. He has observed that the glucose tolerance test may become normal after weight reduction. The experiments were so conducted that one can conclude that body mass of itself is in large part responsible for this effect. Because of

thus, and because these patients did not have hyperglycemia after weight reduction, Newburgh came to the conclusion that they did not have diabetes. The difficulty here is that one thinks in terms of the blood sugar level in dealing with patients and forgets to think in terms of an inherited or acquired pancreatic deficiency. If obesity happens to make this deficiency manifest it causes a revelation of diabetes and not a different type of hyperglycemia.

In this connection the experiment shown in Table 2 may be mentioned. A cat was made mildly diabetic with pituitary extract. It was possible to keep this animal free of glycosuria, with a normal blood sugar when its weight was normal. When it gained weight, it had a diabetic sugar tolerance curve. Several such cycles were observed, and Table 2 shows two of the tolerance tests. The initial weight was 2.15 kg. and 4.7 kg. was definitely overweight. The elevated blood sugars were obvious. After six weeks on a low diet the cat lost weight

TABLE 2

EFFECTS OF WEIGHT REDUCTION IN A CAT WITH MILD PITUITARY DIABETES

Weight kg	Blood Glucose Mg per 100 cc.		
	Fasting	1 Hr	2 Hr
1.7	257	305	351
3.7	97	117	160

and the tolerance test was only a little above normal. The amount of weight lost is comparable to a loss of 44 pounds by a 200 pound patient. These results resemble those seen in obese patients. In this animal biopsies of the pancreas had been taken and damage of the islands of Langerhans had been demonstrated before the tests. Obesity was apparently the added burden which revealed the known pancreatic deficiency in terms of hyperglycemia.

TREATMENT AND THE INCIDENCE OF COMPLICATIONS

One of the largest problems confronting the diabetic whose life is prolonged with insulin is the avoidance of the late complications of the disease. For some conditions such as retinitis there is no sign that this can be done. Concerning other conditions there are reports affording some encouragement. One must recall the long time required to learn the effect of any form of treatment on the late com-

plications It is just twenty-five years since the discovery of insulin and thirty or forty years may well be needed The fact that many well treated diabetics develop gangrene and that occasional negligent diabetics appear to escape trouble can be understood only by more prolonged observation At present only a few of the facts indicating that sustained good control of the disease is beneficial can be mentioned

There are unpublished data to the effect that six out of seven diabetic children who grew less than expected were under poor or only fair diabetic control The authors concluded that their study demonstrated the importance of early and complete control of the disease in order to prevent retardation of growth and development.

In his monograph on the pathology of diabetes Warren⁸ states that prior to 1930 he had never seen a case of diabetes that had lasted five years or more with the patient free from arteriosclerosis, regard less of age. In 1938 he added that since 1930 he had found eleven such cases which failed to show arteriosclerosis In patients under 50 Rabinowitch¹⁰ found that arteriosclerosis was present in some form in 85 per cent of cases in which treatment was by older methods This figure fell to 39 per cent in a later series treated with high carbohydrate diets In a study of diabetics observed for ten years or longer, Naide¹¹ studied the occurrence of arteriosclerosis of the feet He found that 46 per cent of thirty-five patients who were poorly controlled had peripheral arteriosclerosis This was compared to 35 per cent with sclerosis in the fifty-four well controlled patients (blood sugars under 180 mg), admittedly a small difference Goodof¹² reported that of eighty-three patients with intercapillary glomerulosclerosis, fifty had had no treatment for diabetes and ten had used insulin for less than a year. Of fifty-seven patients who had taken insulin, only twenty-three had glomerulosclerosis This means that 40 per cent of the better treated patients had this complication in contrast to 72 per cent of the poorly treated ones

COMMENT AND SUMMARY

These figures are casual selections from the vast literature on diabetic complications and still more time is required to appraise their significance. It is known that well treated patients may develop severe lesions of the heart or feet No single patient can be promised exemption from these bad companions of diabetes Nevertheless, twenty-five years after the discovery of insulin, evidence is beginning to appear

that the degree of control has an effect on some of the late complications as observed in groups of patients

Children must not be made behavior problems because of diabetes. The aged should not be subjected to unnecessary insulin reactions. Even so, exceptions to the best management should be made from necessity and not from indifference. Deviations from the highest standard of regulation should be made wisely but with reluctance.

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PREGNANCY COMPLICATING DIABETES OF MORE THAN TWENTY YEARS' DURATION

PRISCILLA WHITE, M D , F A C P *

BECAUSE diabetes predisposes the pregnant woman to preeclampsia and because it predisposes the patient to vascular disease, it is pertinent to ask the following question Is prolonged duration of diabetes consistent (1) with maternal survival, (2) with maternal well being and (3) with fetal survival?

The experience of this clinic indicates that maternal survival can be assured, that fetal survival approaches normal and that the incidence of preeclampsia can be lowered in typical diabetic pregnancies Thus among 322 consecutive pregnancies in diabetic women studied in this Clinic between January 1936 and November 1946 there was one maternal death due to infectious hepatitis eight weeks after delivery Fetal mortality and the incidence of preeclampsia paralleled an abnormal pattern of the sex hormones of pregnancy Among seventy pregnancies classified as normal by the level of serum chorionic gonadotropin and by the urinary excretion of pregnandiol, the fetal survival was 97 per cent and the incidence of preeclampsia was 1 per cent The sex hormonal pattern was abnormal and uncorrected in sixty two cases In this group the fetal survival was 44 per cent (twenty seven infants) and the incidence of preeclampsia was 50 per cent In 190 cases the abnormal balance of the sex hormones was corrected by substitutional estrogen and progesterone therapy The incidence of preeclampsia fell to 5 per cent and the fetal survival rose to 90 per cent

Control of vascular disease in diabetes has not paralleled the control of preeclampsia in diabetic pregnancies Among 250 of our patients the onset of whose diabetes occurred in childhood, it was found that 70 per cent of the patients surviving twenty years of the disease and who were studied for it had evidence of arteriosclerosis 65 per cent had retinal hemorrhages 40 per cent had hypertension and 55 per cent had nephritis Autopsy on young diabetics since

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1940 have shown intercapillary glomerulosclerosis in all and every autopsy performed at the George F. Baker Clinic on diabetic patients since 1940 has shown some evidence of arteriosclerosis

Preeclampsia is not unlike diabetes in youth in its histopathology, attacking primarily the retina, the kidney glomerulus and the brain. Certain susceptibilities to preeclampsia and certain sequelae of it must be evaluated in relation to the diabetic. Thus it is known that the hypertensive patient is the one liable to preeclampsia and 25 per cent of preeclamptics have permanent vascular damage, that is to say, permanent hypertension. It has been stated that if in preeclampsia, even of mild form, hypertension or albuminuria have lasted for a period of several weeks, permanent postpartum hypertension or albuminuria will probably ensue. Dexter and Weiss have recommended that the pregnancy be terminated if toxemia persists for more than three weeks.

In order to answer the three questions postulated in paragraph one, all diabetic patients whose onset of diabetes occurred in childhood and whose pregnancies were studied by us after twenty years' duration of the disease have been analyzed for fetal wastage and maternal morbidity. Of the fourteen patients so classified, all mothers survived. These fourteen patients had twenty-four pregnancies, thirteen without sex hormone treatment and eleven with sex hormone treatment. The thirteen pregnancies treated without sex hormones resulted in eleven miscarriages, one stillbirth and only one live birth. The eleven pregnancies treated with sex hormones resulted in seven living infants, one stillbirth, two neonatal deaths and one infancy death, or a 63 per cent fetal survival. If the three twenty-five-year duration cases are excluded, in eight of the twenty-year duration cases there were six living children or a total fetal survival of 75 per cent.

Preeclampsia complicated the pregnancies in three of the eight twenty-year-duration cases. In one patient (Case 5110) cerebral manifestations of alarming proportions arose. In the two others (Cases 2975 and 1469) the toxemia was moderately severe. All have permanent hypertension and two albuminuria. Vascular disease was present in these three preeclamptics in the pre-pregnancy state. Thus the first patient (Case 5110) had calcified pelvic vessels, the second (Case 2975) had calcified tibial arteries and retinal sclerosis and the third (Case 1469) had retinal hemorrhages, exudates and retinal sclerosis. Two other patients who did not develop toxemia had vascular disease. In one of these patients an interuterine fetal death occurred, the other had a normal uncomplicated pregnancy (Cases

PREGNANCY COMPLICATING DIABETES A TWENTY FIVE YEARS DURATION

Case	Age	P. before preg.	Pre-Pregnancy			Pregnancy		Insulin—Units Daily		Eyes	Arteriosclerosis		Infant		
			Blood Pressure	F. sugar	Glucose	Lecithin	Pre-Preg. sugar	Pre-Preg. sugar	Tibial		Hb	Outcome	Congenital Abnormalities	Atreticities	
124	25	1	120/70	0	0	4.75	500	70	100	Retinal hemorrhages Arteriosclerosis, Grade 1	0	0	L.B. (C)	Ear notule Birthmark Dermatoma tubercle Congenital heart compatible with life	Grade I
125	27	4	110/60	0	0	4.65	270	30	65	Retinal hemorrhages Arteriosclerosis, Grade 2	+	+	N.N. (C)		Grade IV Fatal
126	28	23	120/70	0	0	4.65	0	65	91	Retinal hemorrhages Prevalent Arteriosclerosis, Grade 2	0	0	L.D. (C)	Congenital heart incompatible with life	Grade IV Fatal

B TWENTY TO 249 YEARS DURATION

127	21	21	70/60	0	0	120/110	4.65	32	64	0	—	L.B. C		0
128	22	22	110/70	0	1.5T	1.2/120	3.65	50	34	+	—	L.B. C		Grade II
129	22	22	120/60	0	10	90/60	3.65	60	76	+	—	R.R. V		—
130	22	22	120/70	0	0	110/70	0	61	65	0	0	L.B. V		0
131	23	23	120/70	0	0	120/70	3.65	54	72	0	0	L.B. C		Grade I
132	23	23	120/70	0	0	120/70	0	60	122	+	+	N.N. C		Fatal
133	23	23	120/70	0	0	110/70	4.65	45	116	0	0	L.B. C		Grade I
134	23	23	120/70	0	0	100/70	0	61	92	0	0	L.B. C		Grade I

1 L.B. = Left Breast
 2 R.B. = Right Breast
 3 V = Ventral Abdomen
 4 C = Cervical Abdomen
 5 N.N. = Navel Navel
 6 L.D. = Left Dorsal

3976 and 11322 respectively) Thus, in this group of patients in whom the duration of diabetes was long, only one of five patients with vascular disease had a completely normal pregnancy

The course of pregnancy after twenty-five years of diabetes was more complicated than before and the fetal survival rate low Thus, among the three patients whose diabetes exceeded twenty-five years, two had preeclampsia in spite of the most modern treatment available and only one of the three infants survived. At the present writing all of these patients have albuminuria and two have hypertension Their cases are here discussed in detail

W C C (Case 2589) had onset of diabetes in November 1920 at the age of 9 years She was treated with undernutrition until June 1923 when insulin therapy was started Her development was dys-harmonious Axillary hair preceded pubic hair Her first menstruation occurred at the age of 17 years Her periods were irregular and averaged three a year At the age of 17 in 1927 she had diabetic coma. Her blood sugar level rose to 480 mg and the carbon dioxide combining power in the blood fell to 8 volumes per cent In 1930 at the age of 20 her weight rose to 130 pounds In 1937 she was admitted to the New England Deaconess Hospital for dental extraction The same year she had a large abscess of the scalp

The patient's first pregnancy occurred in 1938 at the age of 28 Her pre-pregnancy weight was 108 pounds At delivery in the thirty-eighth week her weight had risen to 133 pounds, or a total gain of 25 pounds Her maximum albumin excretion was 180 mg and the maximum blood pressure 170 systolic and 100 diastolic She had moderate ankle edema. Substitutional estrogen and progesterone therapy was inaugurated in the thirty-sixth week of pregnancy The serum prolactin had risen from 200 rat units per 100 cc of serum in the twenty-eighth week to 500 rat units in the thirty-first week It dropped to 200 rat units per 100 cc of serum in the thirty-seventh week, one week after the inauguration of treatment and rose to 1000 in the thirty-eighth week. The patient received ascending doses of progynon B and proluton, from 150,000 I U of progynon B to 450,000 intramuscularly daily and proluton from 10 to 30 mg daily She was delivered by cesarean section of a male infant weighing 7 pounds, 9 ounces

The infant's color was good He cried instantly and the breathing was normal The small fontanelle was closed and his skull was firm The lungs were normal and there was no heart murmur The liver, kidney and spleen were not palpable The mouth and throat were normal Syndactylia of the second, third and fourth fingers of the left hand was present with malformation of the three fingers The fifth finger had a slight contracture The baby's blood sugar was 100 mg

at birth, 80 mg in four hours, 60 mg in eight hours and 70 mg in twelve hours. He received no glucose and remained in a Hess bed with continuous oxygen for forty-eight hours.

In 1940 this patient was found to have retinal sclerosis and a few (two to three) minute hemorrhages in each fundus and blurred edges of the left optic disk. In 1941 the sclerosis was described by Dr William P. Beetham as "slight to moderate" and the hemorrhages as "a few deep hemorrhages in each retina." There was no exudate. We did not see her again until 1944 when she was 33 years of age and her diabetes was of twenty-four years duration. The tibial arteries showed 2 plus calcification. The fundus appeared the same with some areas of waxy exudate. Her chief complaint was convulsive seizures. Lumbar puncture showed normal dynamics and serology. Her total protein was normal, 22.5 mg. per 100 cc and the colloidal gold curve was normal, $543 \pm \pm 0000$. Her blood pressure was 130 systolic and 80 diastolic. The albumin was negligible, 20 mg. The convulsions were unrelated to hypoglycemia. During an attack of aphasia and twitching which occurred at the Deaconess Hospital the blood sugar was found to be 230 mg. An air ventriculogram was negative. An electroencephalogram was normal.

A diagnosis was made of encephalopathy probably with cerebrovascular spasm. The patient was treated with phenobarbital with little improvement. She developed cheilosis and a magenta tongue and was given parenteral vitamin B. In January 1945 at the age of 34 and in the twenty-fifth year of diabetes she reported that she was pregnant. The serum showed a positive test for pregnancy. The neurosurgical consultant thought the cerebral complication was not a contraindication for pregnancy. An x-ray of the pelvis showed calcified pelvic arteries. The patient was most anxious to continue this pregnancy. Her avitaminosis continued and she received substitutional hormonal therapy in the form of daily intramuscular injections of stilbestrol and proli'ron beginning with 5 mg. of each and at each four-week period an additional 5 mg. of each was added until she received a maximum of 10 mg. of each daily. The chorionic gonadotropin rose to 200 units per 100 cc. of serum in the twenty-third, twenty-fourth, thirty-third and thirty-fifth week of pregnancy. All other values after the twentieth week were normal. Her weight rose from the pre-pregnancy level of 109 pounds to 133 pounds, a gain of 24 pounds. She had no hypertension or albuminuria. She had marked edema. Her insulin increased from the level of 65 units in the early part of pregnancy to 91 units at term. The fetal heart was extraordinarily loud. She was delivered of a male infant in the thirty-eighth week of pregnancy.

The child was and remained intensely cyanotic. The cyanosis was

unrelieved by oxygen. No murmur was heard at birth but one could be demonstrated on the fifth day. The infant survived in continuous oxygen for twenty-one days. The autopsy confirmed the diagnosis of congenital heart, classified as complete transposition of the arterial trunks, patent foramen ovale and patent ductus arteriosus. Since delivery the patient has been miserable, has had moderate albuminuria, 100 mg per day, with a maximum blood pressure of 140 systolic and 80 diastolic.

M G C (Case No. 1949) had onset of diabetes in May 1920 at the age of 6 years. She was treated with undernutrition until January 1923 when insulin therapy was inaugurated. She grew normally in stature but her development was retarded. The onset of catamenia occurred at the age of 18 in 1932 in the twelfth year of diabetes. Her periods were irregular with long episodes of amenorrhea. She had hypertrichosis and trunk obesity. The girl progressed well in school, graduated from a secretarial school in 1934 and obtained employment as a private secretary. In 1938 she had a carbuncle, which was incised and drained. An eye examination at that time showed hemorrhages in the right and the left fundus. No albuminuria or hypertension was present. In 1938 at the age of 24 and in the eighteenth year of diabetes she was found to have venous thrombosis of the left retina. In 1939 the arteries were graded as 3. She had edema, macular hemorrhages and new tissue on the disk margins. X-rays of her legs for calcified arteries were negative in 1929 and 1938. In 1943 calcified arteries were demonstrated. Calcinosis was observed in 1929.

In 1941 the patient married and between 1941 and 1945 had five spontaneous abortions. In 1945 her eyes were found to have improved. Her pelvic vessels were not calcified. The blood pressure was normal, 100 systolic and 70 diastolic. There was no albuminuria. She became pregnant in August of that year and was considered a good risk for the pregnancy. In November, the third month of her pregnancy, benztrol and proluton were started. She was given a schedule of ascending doses of 5 mg of each up to the twentieth week, with an additional 5 mg of each every four-week period. The injections were intramuscular and given daily. Her pre-pregnancy weight was 142 pounds and her weight at delivery 172 pounds, a total gain of 30 pounds. She gained rapidly the first month of pregnancy, but her weight was controlled without difficulty later. Her requirement for insulin in the early part of pregnancy was 36 units and rose to 68 units at term. The chorionic gonadotropin level was abnormal as follows: 200 units or above after the twenty-fifth week except in the twenty-eighth and twenty-ninth week of pregnancy. The pregnandiol excretion was normal throughout pregnancy, rising to from 90 to 160 mg after the twenty-eighth week. In the sixth month of preg-

significantly significant albuminuria was observed. The patient was hospitalized in the eighth month of pregnancy because of increasing albuminuria and hypertension. In spite of hospital treatment, progressive toxemia developed with a maximum excretion of 250 mg. of albumin and maximum rise of blood pressure to 170 systolic and 100 diastolic. In the thirty sixth week of pregnancy she was delivered by cesarean section of a female infant weighing 8 pounds, 5 ounces.

The infant did not cry well at birth, had episodes of cyanosis and progressive atelectasis. She survived twenty hours. The clinical cause of death was atelectasis. The autopsy showed a slight intracardiac septum defect, marked atelectasis, marked erythropoiesis of the liver, slight hematopoiesis of the spleen, marked hyperplasia and hypertrophy of the islets of Langerhans and congestion of the brain.

Albuminuria and hypertension persisted after delivery. This patient's emotional problem was solved by the adoption of an infant of another diabetic mother.

LWW (Case No 2563) had onset of diabetes at the age of 7 years in 1921. She received undernutrition therapy until 1922 when insulin treatment was inaugurated. Her adherence to her prescribed diabetic routine was good. She had the typical rejection of the diabetic regimen during her adolescence. She developed no complications but matured late. The first menstruation occurred at the age of 17 and for a while until her marriage in 1935 her periods were irregular and scanty, with long episodes of amenorrhea. In 1936 at the age of 24 and after fifteen years of diabetes the patient had an unsuccessful pregnancy in England. This pregnancy terminated in an intrauterine fetal death in the seventh month. She believed her diabetes was well controlled during this pregnancy.

Her second pregnancy occurred at the age of 26 after seventeen years of diabetes and terminated successfully in 1938. Because of the failure of her first pregnancy the patient was observed closely. Her weight was easily controlled. In the sixteenth week of pregnancy she weighed 125 pounds and in the thirty seventh week at delivery she weighed 135 pounds, a total gain of 10 pounds. Her insulin requirement rose slightly from 78 units daily of divided doses of protamine zinc and crystalline insulin in the twelfth week to 84 in the twenty-eighth week and 95 units in the last month. At no time did she show significant albuminuria. Shortly before delivery her blood pressure rose from her normal of 100 systolic and 70 diastolic to 140 systolic and 80 diastolic. Quantitative chorionic gonadotropin serum levels were determined every two weeks. In the twenty sixth week of pregnancy the level rose to 200 rat units per 100 cc of serum which we consider abnormal. This level persisted until the thirtieth week when it rose to 333 rat units and remained there until the thirty second

week In the thirty-first week estradiol benzoate and progesterone therapy was started This patient was the third pregnant diabetic in our series to be so treated She received 300,000 I U of progynon B and 20 mg of proluton daily from the thirty-first to the thirty-seventh week of pregnancy During this period she was at bed rest She developed severe anemia Her red count fell to 2,500,000 and the hemoglobin to 58 per cent She had many uterine contractions The serum chorionic gonadotropin fell to 200 rat units per 100 cc in the thirty-third and thirty-fourth weeks, but rose to 333 in the thirty-fifth week Although the level fell to 100 in the thirty-sixth and thirty-seventh weeks, cesarean section was elected in the thirty-seventh week and she was delivered of a male infant weighing 6 pounds, 15 ounces

The immediate and postnatal and infancy behavior of this child was completely normal The capillary blood sugar of the infant at birth was 30 mg He received 50 cc of 5 per cent glucose intramuscularly In three hours the blood sugar rose to 100 mg in six hours to 90 mg, in nine hours it was 80 mg and in twelve hours 80 mg The mother had received insulin one hour before delivery Her own blood sugar was 200 mg at the time

At the present writing, with a planned delivery, the last dose of insulin is administered twenty-four hours before delivery and glucose is administered to the mother preoperatively or during the delivery The infant usually receives no glucose This infant showed no apnea, cyanosis or atelectasis There were some slight fibrillary twitchings He did well with breast milk and was discharged on a formula of Karo and milk The patient did not lactate

This woman's third pregnancy terminated successfully in 1940 at the age of 28 after nineteen years of diabetes The course of this pregnancy was not as uneventful as the preceding one The patient's weight rose from 121 pounds in the tenth week to 152 in the thirty-seventh, a maximum gain of 10 pounds in the last four weeks The blood pressure rose to 160 systolic and 90 diastolic just before delivery She had edema and hydramnios The albumin did not rise significantly The insulin dosage was nearly constant, varying from 70 to 80 units daily The excretion of pregnandiol was low from the eighteenth to the twenty-third week, rising from 2 to 14 mg in the twenty-second week of pregnancy The serum prolactin rose to significantly abnormal levels of 200 rat units in the twenty-ninth week, 333 in the thirty-fourth week and to 1000 in the thirty-sixth week Stilbestrol and pranone were prescribed orally in daily doses of 30 and 10 mg, respectively, in the sixteenth week of pregnancy In the twenty-eighth week 5 mg of estradiol as progynon B and 10 mg of proluton were administered daily intramuscularly This dosage was increased to 10 and 40 mg of each daily In the thirty-seventh week of

pregnancy the patient was delivered of a female infant weighing 7 pounds, 15 ounces. The infant had cyanosis and grade II atelectasis for twenty four hours, but improved in constant oxygen and with frequent mechanical stimulation to cry. The blood sugars were completely normal for a newborn infant, namely, 70 mg. at birth, 47 mg in six hours, 78 mg in nine hours and 70 mg in twelve hours.

From 1940 to 1945 the patient led an active life which included tennis, deer and fox hunting. She complained once of a feeling of constriction and pain in the chest while deer hunting and again when she heard that the ship on which her husband was serving as an officer had been hit. In 1944 she developed toxic (tobacco) amblyopia. For years she had smoked more than forty cigarettes daily. She stopped smoking immediately. She had a difficult adjustment to the omission of tobacco but benefited by psychiatric care.

The patient's fourth pregnancy terminated successfully in October 1946 at the age of 34 and after twenty five years of diabetes. This successful termination was not without event, however. In the twelfth week of pregnancy her vascular status was carefully studied. The electrocardiogram was normal. Her blood pressure was 120 systolic and 80 diastolic. The urine contained no albumin. The phenolphthalein excretion was 85 per cent. An x ray of the heart showed slight increase in size but not up to the 50 per cent of the transverse diameter of the chest. The pelvic and tibial blood vessels were not calcified. The toxic amblyopia was relieved. Arteriovenous nicking was observed but her age was now 31. She had a few retinal hemorrhages. Her capillary fragility was increased. She appeared an excellent risk for pregnancy. At the time her weight was 133 pounds, 8 more than the corresponding period in the second and 12 pounds more than in her third pregnancy. Her insulin requirement was approximately the same. This rose gradually to 164 units in the thirty fifth week of pregnancy. By the twentieth week her weight had risen 11 pounds, another 10 by the twenty fourth week, 1 by the twenty eighth week and 12 pounds by the thirty fifth week. The chorionic gonadotropin rose to 500 rat units per 100 cc. of serum in the thirty second week of pregnancy. The pregnandiol excretion was low, 30 mg. in the twenty eighth, 41 in the thirty second, 40 in the thirty third. It rose to normal 86, in the thirty fourth week. Edema developed in the thirty second week and at this time the blood pressure rose to 150 systolic/100 diastolic. With a widely fluctuating daily blood pressure the patient could tell when the level rose to above 140.

In the thirty third week the patient had severe constriction in the chest, moderate pain in the precordium radiating down the left arm to the hand. Five such episodes occurred, associated with pallor, sweating and faint. They were relieved by 1/2 cc grain of nitroglycerin.

In the thirty-fifth week of pregnancy her edema increased, her albumin rose to 510 mg. She became elated and hilarious in proportion to her rising blood pressure. On October 30 the urinary output, though adequate, began to fall. The blood pressure rose to 230 systolic and 120 diastolic, the albumin increased 100 per cent in twenty-four hours and an emergency cesarean section was performed. She was delivered of a male infant weighing 6 pounds, 2 ounces, who recovered within twenty-four hours from a mild grade I atelectasis. The physical examination of the child was completely normal, except for a tiny nodule on the right ear and a small hemangioma of the thigh.

The patient had received ascending doses of stilbestrol and proluton as follows. From the twelfth to the sixteenth week of pregnancy she had received 5 mg. of each daily, intramuscularly, from the sixteenth to the twentieth week, 10 mg. of each intramuscularly, daily; from the twentieth to the twenty-fourth, 15 mg. of each intramuscularly, daily; from the twenty-fourth to the twenty-eighth week, 20 mg. of stilbestrol and 30 mg. of proluton daily, from the twenty-eighth to the thirty-second week, 30 mg. of each daily, from the thirty-second week to delivery, 60 mg. of stilbestrol and 100 mg. of proluton as daily intramuscular injections.

In each pregnancy salt had been restricted, the protein had been 2 gm. per kilogram of body weight and the patient during all of these pregnancies had received one grain of Armour's thyroid extract. No anemia developed in the third or the fourth pregnancy.

The patient complained of angina immediately before and once during the cesarean section. On the third postoperative day at the time of an after-pain and angered by restriction of medication, she had another attack of angina. Her postoperative recovery has been uneventful since that time. Her blood pressure has varied from 160-190 systolic and 100 diastolic.

After seventeen and nineteen years of diabetes, this patient's pregnancies were without undue risk to her or her infant. The pregnancy which occurred in the seventeenth year of diabetes was uncomplicated. That which occurred in the nineteenth year was complicated late. After twenty-five years of diabetes in spite of the most modern care known for these cases, this patient's life was in danger. Her toxemia developed earlier and precipitated angina, presumably due to the coronary insufficiency secondary to long duration diabetes. Each pregnancy was more complicated and hazardous than the preceding one had been.

CONCLUSIONS

From our present data we believe that between twenty and twenty-five years' duration of diabetes, maternal survival, fetal survival and maternal morbidity parallel the degree of pre-pregnancy vascular dis-

case, that after twenty-five years of diabetes the fetal survival is hazardous, the maternal morbidity probable and the maternal survival a gamble. At the present time we are influenced to advise against pregnancy in diabetic women over thirty years of age whose diabetes is of twenty-five years' duration.

SOME CONSIDERATIONS OF ACUTE COMPLICATIONS OF DIABETES

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To tide a diabetic patient over an acute complication with a minimum of risk demands an understanding of metabolic alterations which may develop with great rapidity and which may threaten life. It is not enough to be familiar with the treatment of uncomplicated diabetes because it is a rare diabetic patient who does not sooner or later present his physician with the problems that surround an acute complication. It is of utmost importance, therefore, that students of medicine observe as frequently as possible the management of the various complications of diabetes. It is important to be acquainted with the effects which complications exert on the diabetes and by anticipating them spare the patient needless risk.

The complications of diabetes may be grouped in order of their frequency as follows: acute infections, degenerative disorders, surgical conditions, metabolic disorders—namely obesity and ketosis, and pregnancy. It is our purpose in this clinic to consider some aspects of the treatments for diabetes during acute infections and surgical complications. These complications, by virtue of toxemia, increased total metabolism and other, unknown factors, increase remarkably the need for insulin. For example, one diabetic patient not needing insulin ordinarily, required a peak dosage of 660 units in one twenty-four hour period during an attack of pyelonephritis. Such a great increase is unusual but one cannot predict in advance how much insulin a patient will need to maintain control of the diabetes during acute complications. The amount of insulin given is steadily increased while glycosuria and hyperglycemia persist. Unless special consideration is given to the distribution of the insulin and nourishment, great fluctuation of the concentration of sugar in the blood is almost certain. For the past fourteen years we have employed, at the Pennsylvania and Jefferson Hospitals, a plan of dividing the diet and insulin into four or six equal amounts and spacing them equidistant in the twenty-four hours during the course of acute complications. This plan with

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the use of crystalline insulin only, has greatly increased the simplicity of the treatment and it has reduced remarkably the mortality rate. This plan of therapy has been adopted for use in the United States Army hospitals as outlined in the War Department Technical Bulletin No 168 (issued June, 1945) drawn up by the senior author. For further emphasis on this method the programs employed in several illustrative cases are presented below

The aim is to provide adequate nourishment and yet maintain control of the diabetes, i.e., to keep the blood sugar nearly normal, and by so doing there will be very little glycosuria and little if any acetonuria. To accomplish this aim is to improve the prognosis to a remarkable degree. Uncontrolled diabetes during acute complications is a menace of great proportions

The treatment of any diabetic patient suffering from acute complications is highly individualized. Hence it is difficult to make generalities applicable. It is hoped by presenting a few salient features of several cases that our general plan of therapy will be made clear. We believe that the amounts of protein allowed for our patients in the past have been too small. A wide experience with diets containing large amounts of protein in the treatment of soldiers suffering from hepatitis and battle wounds has left a deep impression of their value and of the lack of harmful effects. As a result it is rare now—for the past year—that we give less than 100 gm of protein daily in the routine treatment of an adult diabetic patient. In fact, considerably more than this amount is commonly employed. Another principle we believe is of great importance, namely that undernutrition should be avoided during acute illnesses—infections, injuries and surgical operations

CASE I. MILD DIABETES AND AN ACUTE FEBRILE ILLNESS

The typically illustrative patient having mild diabetes is middle-aged and overweight. He seeks treatment because of an acute febrile illness complicating the diabetes. The fasting blood sugar concentration prior to the acute complication was normal. It is now elevated and glycosuria is present. The treatment prescribed for the control of the diabetes during the acute phase of the complication may be summarized as follows

Diet: *Protein*—1.5 gm per kilogram of the normal body weight
Carbohydrate—3.5 gm per kilogram of the normal body weight
Total Calories—25 gm per kilogram of actual body weight.

Fat supplies the calories not accounted for by the protein and carbohydrate. The diet for a male, aged 48 years, whose normal average weight is 80 kg but who actually weighs 100 kg. (220 pounds) and is 177 cm. (5 feet, 11 inches) in height, would be protein 120 gm, carbohydrate 280 gm and fat 100 gm (total calories 2500)

The diet is provided in liquid or soft form depending upon the nature and severity of the illness. In prescribing the diet the minimum amount of fluids the patient should take is stated. It is helpful for the dietitian to have this information. The above diet can be provided in as little as 1500 cc. or as much more as is desirable.

For the severely ill patient the diet, given in liquid form, is divided into six equal portions, one of which is given every four hours (see illustrative diet outlined in Table 3). With improvement in the patient's condition the diet is given in soft and liquid form and in four equal portions, one every six hours. Finally, with the restoration of a desire for food and with convalescence well on its way, the diet is divided into three meals and a bedtime nourishment.

Insulin—All diabetic patients require insulin during acute febrile disturbances. The amount needed will vary greatly—from 8 or 12 units every four hours to several times these amounts. For the illustrative patient under discussion it is safe to begin with six units of crystalline insulin before each nourishment. Urine fractions are collected for four or six hour periods according to whether the meals are taken every six or four hours respectively, and are tested for sugar and acetone. Rapid increases—4 to 12 units—are safely made in each dose of insulin until the glycosuria is controlled at which time modest reductions are made in anticipation of the reduction in the need for insulin that accompanies (a) the control of the diabetes and (b) the correction of the acute complication if this end has been reached. The increases in the doses of insulin are greater while large amounts of acetone appear in the urine. Also, the obese patient tends to be especially resistant to insulin. Hence there need be no fear of increasing rapidly the amounts of insulin using the degree of glycosuria as a guide.

With convalescence well established the diet is changed to that which will gradually reduce the patient's weight, e.g. protein 1.25 gm and carbohydrate 2 gm per kilogram of the normal body weight, with sufficient fat to make the total calories 20 per kilogram of the actual body weight. The insulin is steadily reduced and finally omitted, as the obese patient does not need insulin except when acute complications prevail.

Specific therapy directed at correcting the acute complications should receive careful consideration throughout the course of the illness. We refer to sulfonamides, penicillin, streptomycin and other remedies for which there is a field of usefulness in treating the diabetic as well as the nondiabetic patient.

CASE II. SEVERE DIABETES COMPLICATED BY AN ACUTE FEBRILE ILLNESS

To illustrate the treatment for the patient with severe diabetes having an acute febrile complication we select a female aged 17 years, 165 cm (5 feet, 6 inches) in height, and weighing 55 kg (121 pounds) (normal weight 59 kg), receiving 80 units of protamine zinc insulin and 16 units of crystalline insulin each morning and a daily diet of protein 100 gm, carbohydrate 225 gm, and fat 112 gm (2400 calories).

Diet.—The diet in such an instance is shown as follows: protein 2 gm and carbohydrate 4 gm per kilogram of normal body weight, with total calories adequate to prevent undernutrition during the period of acute infection, namely 35 calories per kilogram of actual body weight. Hence the diet would be protein 118 gm, carbohydrate 236 gm and fat 56 gm (1925 calories). The diet may be liquid, soft, or regular and given at four or six hour intervals as in the case of the mild diabetic.

Insulin.—There are different plans of insulin administration but the one that has been most easily manipulated and has yielded best results in our hands is (a) the complete withdrawal of protamine zinc insulin and the use of only crystalline insulin and (b) the substitution of the same total number of units formerly taken, in this case 96 units, as the basic amount but given in multiple doses, i.e., 16 units of crystalline insulin every four hours in the severe cases and 24 units every six hours in the milder or moderating acute infections. This is considered the basic dose. Increases are made as in Case I. When the peak is reached and the diabetes is controlled, reductions in the insulin are usually imperative if hypoglycemic reactions are to be avoided. The rate of reduction goes hand in hand with recovery from the acute infection until the basic dose is approached. With recovery the former diet and insulin are resumed. Slightly more insulin will probably be needed until normal physical habits are restored.

CASE III MODERATELY SEVERE DIABETES AND A SURGICAL COMPLICATION

This patient is a male, aged 22 years, 175 cm (5 feet, 10 inches) in height, weighing 68 kg. (150 pounds) (normal weight 70 kg or 154 pounds), and receiving 54 units of protamine zinc insulin and 12 units of crystalline insulin each morning. His diet is protein 115 gm., carbohydrate 275 gm., and fat 161 gm. (3000 calories)

This patient is admitted for an elective operation—a herniorrhaphy. His fasting blood sugar is satisfactory and traces of sugar are found only in the 4 P.M. to 8 P.M. fraction of urine.

The diet is changed on admission to the hospital to

Protein—15 gm. per kilogram of the normal body weight.

Carbohydrate—3.5 gm. per kilogram of the normal body weight.

Calories—30 gm. per kilogram of actual body weight

By applying these quotas the diet becomes protein 105 gm., carbohydrate 245 gm. and fat 77 gm. (total calories 2100). A moderate reduction of the insulin is made to 44 units of protamine zinc and 8 units of crystalline insulin, although the inactivity incident to hospitalization neutralizes in part the effect which the reduction in diet would be expected to exert.

On the day of operation one quarter of his diet is given in liquid form at 4 A.M.—the operation being scheduled for six hours later (10 A.M.). Twelve units of insulin, approximately one quarter of his former total dose, is given prior to the 4 A.M. nourishment. It may be wise to prevent the remote possibility of a hypoglycemic reaction during the operation by giving intravenously 250 cc. of a 10 per cent solution of glucose in normal saline solution without insulin immediately before operation. This measure is usually unnecessary.

Postoperative orders include the following

12 Noon—Fluids, Saline and Carbohydrate One liter (1000 cc.) of a 5 per cent solution of glucose in normal saline to be given intravenously slowly—8 cc. per minute. *Insulin* Crystalline insulin, 24 units subcutaneously. *Tests* Fractional urines (12 Noon to 4 P.M., 4 P.M. to 8 P.M., 8 P.M. to Midnight, Midnight to 4 A.M., 4 A.M. to 8 A.M., 8 A.M. to 12 Noon) to be tested for sugar and acetone immediately upon the completion of each fraction. Plasma sugar determinations at 5 P.M. and 11 P.M.

6 P.M. Fluids, Carbohydrate If patient cannot take nourishment by mouth one liter of a 5 per cent solution of glucose in distilled water is given intravenously. Insulin crystalline 24 units, is given subcutaneously.

As soon as liquid nourishments are tolerated by mouth the former diet (protein 105 gm, carbohydrate 245 gm and fat 77 gm—total 2100 calories) is provided in liquid form. For the first day this diet is divided into six equal feedings, one being given every four hours with the insulin (crystalline) also divided into six equal amounts, one dose preceding each nourishment. Minor adjustments in the insulin dosage are dictated by the presence or absence of glycosuria in the four hour collections. Frequently, when the early postoperative phase is completely uneventful, the meals and insulin may be given at six hour intervals. By the third or fourth day resumption of the preoperative diet and insulin distribution is usual. A moderate increase of the total insulin over the preoperative dose will be found necessary if the patient is taking his full diet and while he remains inactive. The preoperative insulin dosage can be resumed abruptly with subsequent alterations guided by the results of the examinations for glycosuria.

CASE IV. MODERATELY SEVERE OR SEVERE DIABETES COMPLICATED BY AN ILLNESS WHICH PREVENTS FEEDING BY MOUTH, e.g., AN ACUTE APPENDICITIS WITH PERFORATION

- The diabetes in such a patient gets out of hand rapidly and when seen this type of patient usually has a marked hyperglycemia, glycosuria, acetonuria and, not infrequently, clinical ketosis.

Parenteral feeding with frequent administration of insulin (crystalline) is indicated. The fluid administered should be adequate to prevent the urine volume falling below 1000 cc. From 2 to 10 liters of fluids according to the degree of hydration will be indicated in each twenty-four hours. Recourse to frequent hematocrit determinations is of great value as a guide in avoiding excessive hydration.

Salt Nine grams of salt are normally required in each twenty-four hours but the need is several times this amount if vomiting and ketosis are prominent features.

Glucose A minimum of 200 gm. of glucose is given in each twenty-four hours. More often 300 gm. are allowed and administered intravenously in a 10 per cent solution in distilled water or normal saline as indications dictate.

Protein Protein is provided in the form of whole blood, plasma, concentrated human albumin, hydrolyzed protein, or amino acids. The last two—hydrolyzed protein and amino acids—are commonly employed. Their administration equivalent to 100 gm. of protein daily during the emergency is desirable. They can be administered safely.

in combination with glucose and normal saline at a rate of 8 cc. per minute

Examples of parenteral nourishment recommended by the National Research Council in Convalescence and Rehabilitation Report No. 1, February, 1944, can be utilized with great advantage in treating the diabetic patient during the course of complications. The following is particularly applicable.

"To meet the requirements for the nutrition of a patient who will be unable to take any food or fluids for some days and therefore should receive a nutrient which will provide an adequate amount of some protein substitute

Water	3000 cc.
Casein hydrolysate	100 gm.
Glucose	200 gm.
Salt	10 gm

"This will require 2 liters of 5 per cent casein hydrolysate, 5 per cent glucose solution, and 1 liter of 10 per cent glucose solution, a total of 3000 cc. Since the casein hydrolysate is neutralized it will contain 5 gm of salt per liter, or 10 gm in two liters. Other convenient formulae can be devised by which the volume can be kept below 3000 cc. The selected amount of solution should be injected over a period of about four hours or, preferably, in two equal installments of two hours each. If the patient is given transfusions of whole blood or plasma, the amount of casein hydrolysate will be decreased."

Crystalline insulin is given as frequently as every half hour to the ketotic patient but with the alleviation of this complication a dose every four hours is sufficient to be followed with a dose every six hours as convalescence gets under way, and finally to one dose each of protamine zinc and crystalline or globin insulin each morning.

During acute emergencies every specimen of urine voided is examined for sugar and acetone, and suitable changes in insulin are made accordingly. Glycosuria and acetonuria are more reliable guides to insulin administration than are blood sugar determinations while glucose is being administered intravenously.

CASE V. SEVERE DIABETES AND ACTIVE PULMONARY TUBERCULOSIS

This is the record of A.B., a male aged 50 years, who weighs 50 kg. and is 170 cm. in height. This patient belongs to the relatively small group of patients whose blood sugar level rises and falls with great rapidity with even minor changes in the amounts of insulin given.

TABLE I

THE SIMPLICITY OF THE CONTROL OF A SEVERE DIABETES DURING A FEBRILE PHASE OF AN ACTIVE PULMONARY TUBERCULOSIS

A B, Weight 59 Kg, Height 176 Cm

Diagnoses Diabetes Mellitus, Active Pulmonary Tuberculosis

Date 1946	Blood Sugar (Mg)	Glycosuria and Acetonuria				Insulin (Units)	Diet
		7 A.M. to 11 A.M.	11 A.M. to 4 P.M.	4 P.M. to 9 P.M.	9 P.M. to 7 A.M.		
Oct. 10	308	<u>4+</u> <u>4+</u>	<u>4+</u> <u>1+</u>	<u>4+</u> <u>±</u>	<u>3+</u> <u>0</u>	50 P.Z. 24 Globin } before breakfast	P 100 F 122 C. 225 Cal 250
11		<u>4+</u> <u>0</u>	<u>2+</u> <u>0</u>	<u>4+</u> <u>±</u>	<u>3+</u> <u>0</u>	65 P Z 24 Globin } before breakfast	" " " "
12*	222	—	—	—	—	90 P Z 30 Globin } before breakfast 8 Crystalline (before supper)	" " " "

Diet and Insulin divided into four equal amounts and given at six hour intervals

		3 A.M. to 9 A.M.	9 A.M. to 3 P.M.	3 P.M. to 9 P.M.	9 P.M. to 3 A.M.	Crystalline Insulin				P 100	F 122	C 225	Cal 2500
						3 A.M.	9 A.M.	3 P.M.	9 P.M.				
13		<u>+</u> <u>0</u>	<u>4+</u> <u>0</u>	<u>0</u> <u>±</u>	<u>+</u> <u>0</u>	32	30	20	20				
14		<u>0</u> <u>0</u>	<u>0</u> <u>0</u>	<u>0</u> <u>0</u>	<u>0</u> <u>0</u>	20	20	24	24	"	"	"	"
15		<u>0</u> <u>0</u>	<u>+</u> <u>0</u>	<u>0</u> <u>0</u>	<u>0</u> <u>0</u>	24	24	24	24	"	"	"	"
16		<u>0</u> <u>0</u>	<u>2+</u> <u>0</u>	<u>0</u> <u>0</u>	<u>0</u> <u>0</u>	24	24	24	24	"	"	"	"
17		— —	— —	<u>+</u> <u>0</u>	<u>0</u> <u>0</u>	24	24	24	24	"	"	"	"
18		— —	<u>0</u> <u>0</u>	<u>4+</u> <u>±</u>	<u>0</u> <u>0</u>	24	24	24	24	"	"	"	"
19		<u>0</u> <u>0</u>	<u>0</u> <u>0</u>	<u>0</u> <u>0</u>	<u>0</u> <u>0</u>	24	24	20	20	"	"	"	"
20		<u>0</u> <u>0</u>	<u>0</u> <u>0</u>	<u>0</u> <u>0</u>	<u>0</u> <u>0</u>	20	20	20	20	"	"	"	"
21	130	<u>0</u> <u>0</u>	<u>0</u> <u>0</u>	<u>0</u> <u>0</u>	<u>0</u> <u>0</u>	20	20	20	20	"	"	"	"

Note Underscored figures represent results of tests for acetone P Z = Protamine zinc.
* Records of tests for sugar and acetone for this date were lost.

making the smooth control of the diabetes at any time a difficult matter. The senior author saw him about fifteen years ago but several years elapsed without close medical supervision until in September,

1946, he was found to have an advanced active pulmonary tuberculosis. It will be noted in Table 1 that an attempt was made to control his diabetes by increasing the protamine zinc insulin and the globin insulin and by adding a dose of crystalline insulin. By October 12 he was receiving in all 128 units of insulin. On October 13 and thereafter the diet was equally divided and given at six hour intervals. Note also how promptly the correct amounts of insulin were determined and also that the total amount was reduced by October 20 to 80 units. This satisfactory control was readily accomplished without any apparent abatement in the febrile course of the underlying disorder. However, the ensuing clinical improvement was prompt. This is not a singular result. It is the result almost invariably achieved when the foregoing principles are adhered to.

CASE VI DIABETES—ARTERIOSCLEROTIC HEART DISEASE—CARDIAC DECOMPENSATION—THYROTOXICOSIS—THYROIDECTOMY—PULMONARY ATELECTASIS AND PNEUMONIA

This is the record of a patient under close medical supervision for thirteen years. An Italian woman (M.L.), 56 years of age, 152 cm. (60 inches) in height and weighing 70.6 kg. (155 pounds) was admitted to the Pennsylvania Hospital in 1933, complaining of dizziness and weak spells brought on by the slightest exertion, and anorexia. She had had dyspnea on exertion for four years with a mild degree of edema of the ankles for two years, and she complained of periodic attacks of nonradiating precordial discomfort. The family history was irrelevant except that eight of the nine members of her family were overweight. The patient was obese and had marked hirsutism making shaving necessary once a month. Xanthelasmic lesions were observed on each upper eyelid. There was a prominent diffuse enlargement of the thyroid gland but there was no bruit over the gland. The blood pressure was 146 mm. of mercury systolic and 90 diastolic, and there was a moderate degree of tachycardia (90 to 110).

Laboratory studies revealed glycosuria 1 plus, a normal blood count, serum cholesterol 234 mg. and a fasting blood sugar of 173 mg. per 100 cc. The basal metabolic rates were plus 26 and plus 32 per cent.

The diabetes was controlled by a diet of 1100 calories (carbohydrate 60 gm., protein 70 gm. and fat 55 gm.). Insulin therapy was not necessary. The patient's weight declined from 70 to 60 kg. and she improved symptomatically. The diabetes remained under control and her weight decreased to 55 kg. within six months after discharge. The diet was increased to 1400 and later to 1500 calories and salt restriction was advised because of dyspnea and ankle edema. An increasing tachycardia, a pronounced tremor of the hands, dyspnea

and a basal metabolic rate of plus 47 were found, and continued precordial distress on excitement became noticeable

Readmission in 1933 Patient's weight was 56 kg A complete examination failed to disclose any additional changes except that her pulse rate varied from 100 to 110 and the blood pressure was 154 mm. of mercury systolic and 84 diastolic. Visual field perimetry, roentgenologic studies of the skull and sella turcica, as well as cystoscopic and retrograde pyelographic studies, were negative A mild hypochromic anemia was found She was allowed a 2800 calorie diet (protein 80 gm, carbohydrate 200 gm and fat 186 gm) and the diabetes was controlled by 24 units of unmodified insulin, 14 units before breakfast and 10 units before supper (fasting blood sugar 128 mg per 100 cc.) The patient would not consent to having a thyroidectomy but was given Lugol's solution, 20 drops twice daily, and was discharged to the Outpatient Department where a course of x-ray irradiation of her thyroid gland was given Her basal metabolic rate and pulse rate showed little significant immediate change as a result of the irradiation.

From October, 1933 to March, 1934 the patient's daily calorie allowance was increased to 3500 calories (protein 80 gm, carbohydrate 220 gm) Her weight increased from 55 to 62 kg and she required 40 units of unmodified insulin daily Her basal metabolic rate in March, 1934 was plus 51 per cent Thyroidectomy was again refused. From 1934 to 1937 she had a remission of her symptoms. She felt much better and her basal metabolic rate steadily declined to plus 1 Iodine was not administered during this period Her weight remained about 63 kg although her diet had been reduced to 1600 calories (protein 80 gm, carbohydrate 160 gm) Concurrent with the clinical improvement the insulin requirement decreased to 10 units of protamine zinc insulin daily However, during the next three years the patient's insulin requirement steadily increased to 48 units daily Her diet and body weight remained unchanged The fasting blood sugar values averaged 160 mg per 100 cc and the urine remained consistently free from sugar

After an absence of two and one-half years the patient returned to the Clinic in October, 1942 She was taking 34 units of protamine zinc insulin daily A basal metabolic rate taken in May, 1943 was plus 38 per cent. Thyroidectomy was again refused and in March, 1944, she was admitted for thiouracil therapy Laboratory studies revealed a mild hypochromic anemia, 1 plus albuminuria, a normal blood cholesterol, and a basal metabolic rate of plus 32 per cent Except for a Q_3 wave the electrocardiogram was within normal limits The patient was given thiouracil, 0.2 gm, three times daily. The dosage was increased to 0.3 gm, three times daily, without untoward effect, and she was discharged taking 0.4 gm a day On discharge her

basal metabolic rate was plus 20, her pulse rate 80, and blood pressure 140 mm. of mercury systolic and 84 diastolic.

From April, 1944 to April, 1945 the patient took thiouracil in doses varying from 0.1 to 0.6 gm daily without untoward effects. During this period she gained 5 kg. in weight and her diabetes remained under excellent control on 22 units of protamine zinc insulin each morning. The thiouracil was discontinued in April, 1945.

In May, 1945, the patient was readmitted to the hospital for the fourth time. She was suffering from dyspnea and was orthopneic. She had a fever 101° F (oral), and coughing spells. She was cyanotic, dyspneic, and complained of severe headache and discomfort over the lower chest anteriorly and epigastrium, together with painful swollen legs. She presented the clinical picture of congestive cardiac failure with bilateral pleural effusions. The pulse rate was 130 per minute and there was a moderate degree of hepatomegaly and a 2 plus edema of the ankles and legs. Fluid (800 cc.) withdrawn from the left pleural space was bacteriologically sterile. There was a leukocytosis (34,000) and a 1 plus albuminuria. She was digitalized and given sulfadiazine orally. The symptoms of cardiac decompensation subsided promptly. Her diabetes remained satisfactorily regulated on a 1400 calorie diet (protein 90 gm, carbohydrate 120 gm) with 28 units of protamine zinc insulin. Inasmuch as her basal metabolic rate had increased to plus 37 per cent thiouracil, 0.6 gm daily, was resumed.

In January, 1946 an electrocardiogram revealed RST segment changes indicative of a damaged myocardium with left ventricular strain. Digitalis therapy was continued with thiouracil (0.6 gm. daily) and her diabetes was satisfactorily controlled with a 1600 calorie diet which she had taken for many years, and 35 units of protamine zinc insulin. During this period she complained of a choking sensation from pressure on the trachea caused by the goiter. The body weight and appetite had been maintained and there were no symptoms of congestive heart failure. Because of increasing tracheal compression the patient entered the hospital for the fifth time in June, 1946. The thyroid gland was tremendously enlarged. A faint bruit was heard over the right lobe anteriorly. She presented evidence of arteriosclerotic heart disease with a moderate enlargement of the heart, a normal sinus rhythm and mitral insufficiency but with no signs of cardiac decompensation, and the diabetes was well controlled. Laryngoscopic examination disclosed no abnormalities of the vocal cords. Laboratory studies revealed a normal blood picture, a 2 plus albuminuria and a basal metabolic rate of plus 15 per cent.

Under general anesthetic a total thyroidectomy was performed. The patient's postoperative course was complicated by a pulmonary atelectasis which necessitated bronchoscopic aspiration. An attack of

bronchopneumonia ensued but it responded favorably to penicillin therapy. Twelve days postoperatively the serum calcium and phosphorus were 8 and 5 mg per 100 cc. respectively and the basal metabolic rate was minus 12 per cent. She was improved clinically. Insulin therapy, no longer necessary, was discontinued. A fasting blood sugar taken prior to discharge from the hospital was 128 mg per 100 cc. and there was no glycosuria. The trend toward increased allowances of protein is exemplified in this patient's present diet (November, 1946), the values being protein 100 gm, carbohydrate 150 gm and fat 67 gm (1700 calories).

This case has been presented to illustrate a rather complicated clinical career of a diabetic patient. It illustrates that diabetic patients with much against them clinically can survive cardiac decompensation, thyrotoxicosis, thyroidectomy, postoperative pulmonary atelectasis and pneumonia. It is imperative if these results are to be obtained that appropriate attention be given to the control of the diabetes, to the nutrition of the patient, and to the specific therapies indicated for the correction or control of the other complicating disorders. Even at this late date there is too much despair in dealing with serious complications in diabetic patients. This despair is unwarranted.

CASE VII. DIABETES MELLITUS—ACUTE PYELONEPHRITIS

This white female patient (M.L.), aged 68 years, weighing 50 kg. and being 160 cm in height, was in comparatively good health until August, 1945 when she experienced a progressively severe pruritus vulvae, extreme thirst, polyuria, nocturnal frequency, malaise and polydipsia. Her family physician made a diagnosis of diabetes and prescribed an undernutrition diet on which she lost 5 kg in two months. Another physician advised her to take a liberal unrestricted diet and prescribed 30 units of protamine zinc insulin before breakfast daily. After a brief period of symptomatic improvement and gain in weight, the patient became ill again and was discovered to have an infection in the urinary tract with fever, malaise, mild abdominal discomfort, nausea and vomiting, and was advised to seek hospital care. She was admitted to the Pennsylvania Hospital on the evening of May 28, 1946.

The patient had taken 30 units of protamine zinc insulin on the day she entered the hospital. She had had neither breakfast nor lunch. She was weak, slightly drowsy and dehydrated, and presented evidence of a moderate loss of weight. Her temperature was 99.6° F (oral), pulse rate 90, and her respirations were normal. Her blood sugar and carbon dioxide combining power were 334 mg. per 100 cc. and 51 volumes per cent respectively. Examination of her urine

revealed a 4 plus glycosuria, 1 plus acetoneuria, numerous pus cells, and many gram negative rods identified subsequently as *Escherichia coli*

TABLE 2

DIABETES AND PYELONEPHRITIS (CASE VII) THE PROMPT CORRECTION OF MODERATE HYPERGLYCEMIA AND THE GREAT FLUCTUATION IN THE BLOOD SUGAR LEVEL (SEE TEXT) BY EQUAL DIVISION AND DISTRIBUTION OF DIET AND INSULIN

Date 1946	Blood Sugar (Mg.)	Glycosuria and Acetonuria				Insulin (Units)	Diet			
		9 P.M. to 7 A.M.	7 A.M. to 11 A.M.	11 A.M. to 4 P.M.	4 P.M. to 9 P.M.					
May 31	238	4+ 0	3+ 0	3+ 0	2+ 0	34 protamine 20 crystalline } before breakfast	P 90	F 58	C. 200	Cal. 1500

Diet and Insulin divided into four equal amounts and given at six hour intervals

		8 A.M. to 2 P.M.	2 P.M. to 8 P.M.	8 P.M. to 2 A.M.	2 A.M. to 8 A.M.	Crystalline Insulin				P	F	C.	Cal.
						8 A.M.	2 P.M.	8 P.M.	2 A.M.				
June 1	364	3+ 0	4+ 0	4+ 0	0 0	15	15	15	15	"	"	"	"
2		0 0	0 0	0 0	0 0	15	15	15	15	"	"	"	"
3	187	0 0	0 0	0 0	0 0	15	15	15	15	"	"	"	"
4		0 0	0 0	0 0	0 0	15	15	15	15	"	"	"	"
5		2+ 0	0 0	0 0	0 0	15	15	15	15	"	"	"	"
6		0 0	0 0	0 0	0 0	15	15	15	15	"	"	"	"
7		0 0	0 0	0 0	0 0	15	15	15	15	"	"	"	"
8		0 0	0 0	0 0	0 0	15	15	15	15	"	"	"	"
9		0 0	0 0	0 0	0 0	15	15	15	15	"	"	"	"
10	169	0 0	0 0	0 0	0 0	15	15	15	11	"	"	"	"

Note: Underlined figures represent results of tests for acetone

The fasting blood sugar level and carbon dioxide combining power were 145 mg. per 100 cc. and 50 volumes per cent respectively on the following morning May 29, the patient having received 20 units of crystalline insulin the previous evening. Her temperature was 102° F

(oral), but she did not appear acutely ill. The urine fraction collected between 9 P.M. on the previous night and 7 A.M. contained a 2 plus reaction for sugar and 1 plus acetone. She was given 30 units of protamine zinc insulin followed by the breakfast quota of a 1500 calorie diet (protein 90 gm, carbohydrate 200 gm, fat 38 gm) which had been divided into three equal feedings and a bedtime nourishment. A blood sugar determination taken before the noon feeding was 334 mg per 100 cc. Following her noon feeding, part of which had been rejected, the urine contained large quantities of sugar and gave a 2 plus reaction for acetone. She was again given 20 units of crystalline insulin before supper.

On the following morning (May 20) the patient's fasting blood sugar was 98 mg per 100 cc and her urine contained a trace of sugar but no acetone. She was then given 34 units of protamine zinc insulin and 20 units of crystalline insulin, injected separately before breakfast, and the three equal feedings schedule was continued. Throughout the night her urine contained 3 plus sugar but no acetone, and the fasting blood sugar obtained the next morning (May 31) was 238 mg per 100 cc. One day later (June 1) it was decided that prompt and better control of this patient's diabetes could be achieved by the adoption of the interval feeding program with the same diet divided into four equal feedings served at six hour intervals and with a uniform dosage of crystalline insulin administered before each feeding. The validity of this principle is shown in Table 2.

THE SURGICAL DIABETIC

Preoperative Preparation.—The preparation of every patient for a major surgical procedure is of the utmost importance. We refer to the control of the diabetes and to the preparation from the nutritional standpoint. We cannot believe that a diabetic receiving a minimum of protein and calories for years can be as good a risk as one with a positive nitrogen balance and receiving adequate calories to prevent undernutrition when subjected to acute infections or surgical measures.

Diet.—Several days or a week (when time permits) preoperatively the adult patient has especially close supervision of his or her diet to make certain that the prescribed amounts of food are actually ingested. If there are "leftovers" an equivalent amount is prepared in liquid form and the patient takes it before the next meal. Unless such a check is made it is remarkable how great the deficiency in intake may become. This feature, throughout the many hospitals which the

senior author has had the opportunity of visiting, receives inadequate attention

A more or less standard diet during the preoperative period is as follows

Protein—a minimum of 100 gm, or 1.75 gm per kilogram of the normal body weight, whichever is greater

Carbohydrate—3 gm per kilogram of the normal body weight

Total Calories—35 calories per kilogram of actual body weight

Fat makes up the balance of calories not provided by the protein and carbohydrate.

The preoperative diet for the elective surgical patient is given in three equal meals with a bedtime nourishment containing 10 to 15 gm of carbohydrate, e.g., a cup of milk and three graham crackers or one slice of bread with butter

In the cases of toxic or febrile complications the diet is divided into four or six equal feedings according to the severity of the condition, and given at six or four hour intervals as mentioned earlier in this paper in dealing with acute infections. The diet is fortified with multivitamins* and these, during these acute pre- and postoperative phases, are given intramuscularly, or intravenously in conjunction with intravenous infusions

Insulin—It may be possible to control the diabetes preoperatively by merely increasing the amounts of insulin given without changing the brands or increasing the number of doses. However, when four or six equal feedings equally spaced in the twenty four hours are employed, crystalline insulin alone is used and divided equally in accordance with the number of feedings

On the day of operation feedings by mouth in general are discontinued at least six hours before the anesthetic is administered. The last preoperative meal is given in liquid form preceded by an injection of insulin the amount being one quarter of the previous day's requirement

Postoperative Management—During phases when oral feeding is not allowed appropriate amounts of carbohydrate, as outlined earlier, are given intravenously at six or eight hour intervals and the protein needs may be satisfied by the administration of amino acids given in the same manner (see p. 412). Crystalline insulin is given at four hour intervals. When oral feeding is permissible the diet for a day or two is given in six feedings (at four hour intervals), then changed to

* Solubil prepared commercially by Upjohn & Company has proved especially satisfactory. The contents of one ampule daily are recommended.

four feedings at six hour intervals with insulin given before each. An illustrative liquid diet divided in this manner is presented in Table 3. Finally when convalescence is well under way—usually in three or

TABLE 3
LIQUID DIET (SIX EQUAL FEEDINGS)*

	Gm.	Protein	Fat	Carbohydrate
<i>8 A M</i>				
Skimmed milk	240	8		12
Powdered skimmed milk	18	6		9
Cereal (dry) gruel	20	3		16
Butter	8		7	
Tomato juice	166			5
		<u>17</u>	<u>7</u>	<u>42</u>
<i>12 Noon</i>				
Skimmed milk	240	8		12
Powdered sk milk, water $\frac{1}{2}$ to $\frac{3}{4}$ cup	18	6		9
20% cream	40	1	8	1
Purée vegetable (peas)	50	2		4
Grape juice	90			16
		<u>17</u>	<u>8</u>	<u>42</u>
<i>4 P M</i>				
Ginger ale	125			20
Skimmed milk	240	8		12
Powdered skimmed milk	18	6		9
20% cream	40	1	8	1
Egg white	20	2		
Vanilla				
		<u>17</u>	<u>8</u>	<u>42</u>
<i>8 P M</i>				
Orange juice	100			12
Egg white	30	3		10
Glucose	10			9
Skimmed milk	180	6		9
Powdered skimmed milk	18	6		9
20% cream	40	1	8	1
		<u>16</u>	<u>8</u>	<u>41</u>
<i>12 Midnight</i>				
Egg, whole	50	7	5	
Egg, white	30	3		
Powdered skimmed milk	18	6		9
Water $\frac{1}{2}$ to $\frac{3}{4}$ cup				
Cream	15		3	
Lactose	33			33
		<u>16</u>	<u>8</u>	<u>42</u>
<i>4 A M</i>				
Broth, $\frac{1}{2}$ cup				
Gelatin	6	5		124
Orange juice	200			18
Lactose	18			
Egg	50	7	5	
Gelatin	6	5		
		<u>17</u>	<u>5</u>	<u>42</u>
Total		100	44	251

* This is adequate in all respects except the vitamin B complex

four days after operation—the patient's diet and insulin distribution employed before the complication are resumed with suitable changes in the amounts of insulin given to maintain satisfactory control of the diabetes

It is worth emphasizing that patients having a limb or part of a limb amputated do not need to miss a meal—that no intravenous therapy may be needed and that these patients may sit up six hours after the surgical procedure is terminated.

Anesthetic.—Local, regional and spinal anesthetics are best suited for diabetic patients undergoing surgery. Nitrous oxide and ether may be used when the nature of the operation necessitates general anesthesia.

QUESTIONS AND ANSWERS

STUDENT *Why do you prescribe the protein according to the normal body weight and the total calories according to the actual body weight during the acute complication in Case I?*

ANSWER Protein metabolism is not increased by obesity, hence it would be illogical to base the protein requirement on the actual weight of an obese individual. Total calories on the other hand are intimately associated with the actual weight. To prevent an obese patient from losing weight, more calories are needed than would be required to prevent a loss of weight in a patient whose weight is normal. We do not consider it a good practice to attempt to reduce a patient's weight while reparative tissue changes are in process or if the patient is attempting to develop an immune response to an acute infection. It is well to correct the infection, then reduce the body weight.

STUDENT *Two grams of protein per kilogram of the normal body weight were prescribed. Is this not higher than is usually allowed?*

ANSWER Yes it is. The part played by protein in tissue repair and its importance in developing an immunity to infective agents are well known. Too often these properties are overlooked in prescribing diets. The surgeons have taken the lead in this field and have produced convincing evidence of the increased need for protein following shock, injuries, surgery and especially when there is an inadequate caloric intake. There is no doubt that greater attention will be given this aspect in the treatment of the diabetic patient in the future. Larger amounts of protein than are usually allowed are indicated.

STUDENT *When the seriously ill patient is receiving feedings and insulin at four hour intervals would it be permissible to omit the 4 A.M. feeding?*

ANSWER No. The simplicity of the plan and its effectiveness would be sacrificed. Having an eight hour period without food and insulin inserted in a twenty four hour period when other intervals between nourishments and insulin are only four hours breaks the uniformity

of treatment and permits wider fluctuations in the blood sugar value and makes it much more difficult to predict where the blood sugar levels are at given times. A patient ill enough to warrant this four hour interval plan will be wakeful. When this is not the case it is time to shift to six hour interval feedings and insulin administrations.

STUDENT: I have seen patients treated with protamine zinc insulin during complications. Is this wise or necessary and does it simplify the treatment?

ANSWER: Some excellent authorities leave the basic dose of protamine zinc insulin unchanged but give crystalline insulin frequently and in sufficient amounts to keep the diabetes under control. We prefer a short-acting insulin as one easier to manipulate and one with which changes are more readily predictable than when two insulins are employed. The use of two insulin preparations makes the treatment more complicated.

STUDENT: What is the best way of regulating the amount of insulin given during acute complications of diabetes?

ANSWER: The examination of fractional urine specimens for sugar and acetone provides the most practicable guide in meeting the insulin need of the patient. When these become free from sugar, modest reductions are usually indicated. These reductions may be guided by blood sugar determinations secured morning and evening during the emergency period.

STUDENT: I notice there is different timing for the collection of fractions of urine. Would you make the indications for each clear?

ANSWER: Yes, for the uncomplicated diabetic and for the patient whose diabetes is not out of control preoperatively and who is maintained on one or two doses of insulin, fractions of urine are collected from 7 to 11 A.M., from 11 A.M. to 4 P.M., from 4 P.M. to 9 P.M., and from 9 P.M. to 7 A.M. For the patient receiving meals and insulin every six hours, 6 A.M., 12 Noon, 6 P.M., and Midnight, four fractions are collected: 6 A.M. to 12 Noon, 12 Noon to 6 P.M., 6 P.M. to Midnight, and Midnight to 6 A.M. Similarly for the patient getting nourishment and insulin at four hour intervals six four hour fractions of urine are collected and examined for sugar and acetone.

STUDENT: What, in your experience, comprises the greatest improvements in the treatment of the diabetic patients having acute complications?

ANSWER: Insulin, of course, was the greatest advance. Then came the improvement in nutrition allowed by increased total calories. Next was the trend to more liberal allowances of carbohydrate. Then, in

our experience, the next advance was the adoption in 1932 of the equal division and distribution of diet and insulin. This plan is simple and when followed carefully is of great value. Next came the appreciation of the need of these patients for more liberal allowances of protein—a consideration widely neglected. The appreciation of the value of vitamins, of course, is of outstanding importance. Also, the employment of early ambulation, sulfonamides, penicillin and streptomycin have been epochal advances.

CLINICAL IMPLICATIONS OF ALLOXAN DIABETES

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When alloxan, a pure chemical substance related structurally to uric acid, is injected into rabbits,¹ rats,² dogs,³ monkeys,⁴ pigeons⁵ or turtles,⁶ it destroys the islets of Langerhans in the pancreas and produces diabetes. Animals with diabetes so produced have clinical symptoms which are indistinguishable from those of human diabetes. Polydipsia, polyuria and polyphagia may be marked and there is often extreme weight loss if the diabetes is not controlled with insulin. One such diabetic rat weighing 120 gm excreted 72 cc of urine in twenty four hours in contrast to the usual 3 to 5 cc. Such animals become listless and dehydrated.

Rabbits and rats with severe alloxan diabetes, if untreated with insulin, may develop diabetic acidosis and coma and may present blood chemical changes similar to those found in humans with diabetic coma. Lowering of the carbon dioxide content of the blood,⁷ marked lipemia,⁸ hypercholesteremia,⁹ acetoneuria¹ and an increase of the blood inorganic phosphates¹⁰ have all been reported. In markedly lipemic rabbits lipemia retinalis is easily seen. Kendall and his co-workers⁹ report that rabbits dying in diabetic coma have been found to have hypercholesteremia reaching 780 mg. per 100 cc and hyperlipemia ranging to 18.5 gm per 100 cc.

Clinically, animals dying in diabetic coma often have deep respirations, simulating the Kussmaul breathing of the diabetic coma patient.

Diet—Alloxan diabetic rats placed on a high fat diet containing 90 per cent margarine and 10 per cent casein plus a salt mixture show a marked decrease and finally a disappearance of glycosuria.¹¹ When the original high carbohydrate diet is given again, however, glycosuria returns. A sudden change from a high carbohydrate to a high fat diet produces ketonuria in varying degrees in the rat and similar ketonuria has been reported in human diabetes when such a change is made in the diet. It has further been shown by Mar

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tness¹² in Houssay's laboratory that a high fat diet increases the sensitiveness of young white rats to the diabetogenic action of alloxan, whereas, a high protein diet makes the rat more resistant than normal to alloxan

It is known that hyperthyroidism affects the blood sugar in humans and for this reason in the George F Baker Clinic a diagnosis of diabetes is not made in a person with hyperthyroidism unless the blood sugar reaches a level of 200 mg, in contrast to the usual diagnostic level of 170 mg. The effect of thyroid is likewise evident in the rat given alloxan, for a thyroidectomy previous to the injection of alloxan makes the rat much more resistant to its diabetogenic action.¹³ In contrast, the feeding of thyroid extract to rats increases their sensitivity to the diabetogenic action of alloxan. Thiouracil has an even greater inhibitory effect than thyroidectomy.¹⁴

Alloxan diabetic animals have been valuable in studying the vitamin requirements in diabetes. Lowry and Hegsted¹⁵ present evidence that rats made diabetic with alloxan showed no increased tendency to develop signs of thiamine deficiency when placed upon a thiamine deficient diet as compared with the normal rat. They further state that the action of thiamine is not impaired in the diabetic animal and from their experiments conclude that the requirement of this vitamin is no greater than that of normal animals.

Cataracts.—The animal made diabetic with alloxan tends to develop diabetic cataracts, especially if the diabetes is severe and uncontrolled with insulin.⁸ In rats definite cataracts can usually be detected as early as one or two months and often become mature, frequently with complete blindness, in two to four months. A similar cataract may at times be seen in diabetic humans, especially among younger persons whose diabetes is severe and imperfectly controlled. In the diabetic animal attempts have been made to determine the cause of these lens changes. Some claim that diets deficient in riboflavin or tryptophane may produce cataracts in animals. It has recently been shown¹⁶ that the supplementary injection of riboflavin, pyridoxine, thiamine or tryptophane does not prevent the development of cataracts in rats with severe alloxan diabetes. Animals with mild diabetes or with diabetes partially controlled with insulin show much less tendency to develop cataracts and when they do occur they tend to remain immature.

PATHOLOGY OF ALLOXAN DIABETES COMPARED WITH HUMAN DIABETES

The outstanding pathological finding in animals given alloxan is the striking effect upon the islets of Langerhans in the pancreas. If the proper dose is used the damage to other organs is usually minimal and reversible. As early as five minutes after injection a slight reduction in the number of granules in the beta cells (which presumably form insulin) may be seen, and by the end of one hour the nuclei of the central beta cells have become shrunken and early cytoplasmic disintegration is visible. Within twenty-four hours the central beta cells are completely destroyed and the center of the islets contains only debris surrounded by a collar of intact alpha cells. The chronic lesion found after two months shows islets smaller than normal and composed almost entirely of alpha cells.

The production of diabetes by the injection of repeated small doses produces a somewhat different picture. Some of the islet cells may appear normal, others may show loss of granules and pyknosis of their nuclei, associated occasionally with clear vacuoles in the cytoplasm, the so-called "hydropic change." Occasionally, mitotic figures are seen in the beta cells. Mitotic figures in acinar cells and in the lining epithelium of the small pancreatic ducts are also occasionally observed. Significant changes in other organs are essentially confined to necrosis of the epithelium of the renal tubules, especially in rats, fatty infiltration of the liver in dogs and small foci of necrosis and occasional mitotic figures in the adrenal glands.

A comparison of these changes with the pathological alterations in human diabetes reveals, at first glance, but few points of similarity. Acute necrosis of the islet cells is exceedingly rare in human diabetes. Hydropic degeneration has been described but is infrequent, occurring in approximately 5 per cent. The most frequent lesions found in the human diabetic pancreas, according to Warren,¹⁷ are hyalinization of some of the islets in approximately 40 per cent and fibrosis in some islets in approximately 25 per cent. In approximately 25 per cent no pancreatic lesion has been demonstrated. A few pancreases show hydropic degeneration, hypertrophied islets or lymphocytic infiltration in some of the islets. Certainly the acute pathological changes found after alloxan do not simulate this picture, although one would not expect acute changes produced with a chemical substance to resemble chronic changes seen after years of diabetes. The opportunity to examine a human pancreas within a few days after the onset of diabetes is indeed rare. It should be emphasized, perhaps, that the con-

dition of the beta cells in the human pancreas and their number relative to the number of alpha cells have not been adequately investigated, due to the lack of useful staining methods for differentiating beta and alpha cells. Perhaps the further development of such methods will permit extension of the work of Gomori,¹⁸ who reported a marked reduction in the ratio of beta to alpha cells in a few human diabetic pancreases studied with special stains. If such findings can be confirmed, there may prove to be more similarity between the lesions of human and chronic alloxan diabetes than is now apparent.

Some of the chronic degenerative changes frequently found in various organs in human diabetes, such as intercapillary glomerulosclerosis and severe arteriosclerosis, have not been reported in animals made diabetic by means of alloxan. Such lesions, however, may require a long period for their development and, if animals with alloxan diabetes are kept alive for years, these changes may eventually be found.

The Effect of Alloxan on Humans.—Alloxan has been given to humans with varying results. Brunschwig and his associates^{19, 20} were the first to administer alloxan to humans, all of whom had evidence of metastatic carcinoma, and one had an islet cell carcinoma with clinical hyperinsulinism. In three patients little or no change in the blood sugar was observed after the patients received alloxan. A fourth patient experienced a chill, nausea and cyanosis lasting for several hours but developed no evidence of diabetes. A fifth patient who received the largest single injection of this group (600 mg per kilogram) died six hours after the termination of the injection. Approximately three hours before death the blood sugar had fallen to 16 mg per 100 cc., and there were clinical signs of an insulin reaction. These, however, disappeared with intravenous 50 per cent dextrose. At postmortem examination a microscopic study of the liver showed rather diffuse degenerative changes in the hepatic cells. The pancreas revealed questionable evidences of injury to a number of cells in some of the islets, although many islets were not affected. Of course, evidence of widespread carcinoma was found.

The sixth patient who received alloxan had an islet cell carcinoma with metastasis and evidence of hyperinsulinism. He received several series of alloxan injections and after each there was a period of freedom from attacks for ten to twenty-one days. This patient finally died and on postmortem examination no evidence of damage to the normal islet cell tissue of the pancreas nor of the metastatic nodules in the liver could be found.

The extreme danger accompanying the administration of alloxan to humans is illustrated by a case of islet cell carcinoma with metastases treated with alloxan by Rynearson²¹. This patient received alloxan and died a short time later with pathological evidence of extensive liver necrosis, presumably due to the toxic effect of alloxan. The blood sugar in this patient reached 428 mg per 100 cc. before death. Conn²² presents evidence that alloxan may destroy the normal islets of Langerhans in the pancreas. His patient, suffering from hyperinsulinism, was treated with alloxan and although there was a marked change in the character of the glucose tolerance curve, hypoglycemic attacks continued. At exploration an islet cell tumor was removed from the pancreas, but histological study failed to reveal damage to the tumor cells. A biopsy of the pancreas nonetheless revealed definite damage to the islets of Langerhans. Following operation the patient was diabetic and has remained so for a period of three months' observation.

Recently Talbot and Bailey²³ treated an 8 month old baby girl who had evidence of hyperinsulinism with alloxan. This child's fasting blood sugars were constantly low, frequently below 30 mg per 100 cc., and hypoglycemic convulsions occurred almost daily. Laparotomy failed to reveal a pancreatic adenoma. Accordingly a series of injections of alloxan was instigated, beginning with 10 mg. per kilogram and gradually increasing to 100 mg. After seven injections evidence of hypoglycemia disappeared and the fasting blood sugar was normal. After an interval of three weeks a tendency to hypoglycemia returned and, accordingly a second series of eight alloxan injections were given. Following the latter all evidence of hypoglycemia disappeared and the child has remained free from evidence of hyperinsulinism to the present time, eleven months later. Nevertheless, the use of alloxan in humans at present is to be condemned, for its administration is accompanied by extreme danger. Even in cases of hyperinsulinism the chances are great that an islet cell tumor can be removed at operation and successfully removed with complete cure. Only in the extremely rare case of hyperinsulinism where the islet cell tumor can only be removed by a subtotal pancreatectomy is usually the case.

DISCUSSION

The injection of alloxan into the pancreas of a rat destroys the islets of Langerhans and the resulting diabetes is indistinguishable from that of the human. The alloxan diabetes is

duced can be modified by diet or insulin. Diabetic complications which may be seen in humans, including diabetic acidosis and coma and diabetic cataracts, are evident also in animals made diabetic with alloxan.

A comparison is made of the pancreatic pathology of alloxan and human diabetes.

Alloxan injected into humans may destroy the normal islets of Langerhans. Islet cell adenomas, however, appear resistant to its action. Furthermore, since alloxan may produce liver necrosis and fatal toxic reactions, its use in humans is not advised.

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SUMMER CAMPS FOR DIABETIC CHILDREN

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For a number of years the George F. Baker Clinic of the New England Deaconess Hospital has sponsored camps for diabetic children. These camps have been financed in part by two church organizations, The Association of Universalist Women and The Unitarian and Other Liberal Christian Women, in part by the children and in part by the Diabetic Fund.

The object of the camps is threefold. The first of these is the readjustment of treatment which includes regulation of diabetes, instruction in the care of the disease and the psychological adjustment to diabetes in the presence of other diabetes. The second object is the provision for the recreational advantages of a well organized summer camp. This program consists of swimming, handicraft, nature craft, folk dancing, baseball, archery and other activities. The third object is the protection of the parents of the children who are given a well earned respite from the grave responsibility which is theirs.

The staff of the camp consists of two departments. The recreational department includes a camp director, a financial secretary, an adequate corps of picked counsellors, a complement of cooks and kitchen help. The medical staff consists of two or more physicians from the George F. Baker Clinic who make weekly visits and such emergency calls as are necessary, two nurses and one laboratory technician trained at the George F. Baker Clinic.

In addition to the physical requirements of any summer camp, a camp for diabetic children must provide a laboratory and must include a plan for weighed diets. Essential tests include those for acetone, quantitative and qualitative tests for sugar, capillary blood sugars and white blood counts. Weighed diets were originally served cafeteria style. Errors were minimized by the weighing of hot foods at the table. This task is done by a regular counsellor. Cold foods are weighed and served at each child's place before the meal.

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TABLE I
SUMMARY OF TREATMENT OF DIABETES--BOYS

Age, Years	No	First Day						Sixth Day					
		Insulin, Units Cryst. Prot. Total Zinc	Gm Glucose in 24 Hours	C Gm	P Gm	F Gm	Calories	Insulin Units Cryst. Prot. Total Zinc	Gm Glucose in 24 Hours	C Gm	P Gm	F Gm	Calories
4-4 9	2	2 + 10 12	10	143	67	77	1533	3 + 14 17	0	143	67	77	1533
5-5 9	2	10 + 12 22	23	157	78	82	1678	17 + 22 39	5	157	78	82	1678
6-6 9	3	8 + 12 20	7	173	77	88	1792	10 + 14 24	2	173	77	88	1792
7-7 9	2	4 + 23 27	4	169	75	86	1750	2 + 19 21	2	174	77	88	1796
8-8 9	5	8 + 20 28	10	182	80	90	1858	8 + 20 28	3	186	84	92	1908
9-9 9	12	9 + 20 29	9	190	87	91	1954	11 + 21 32	8	199	90	96	2020
10-10 9	7	6 + 18 24	13	204	100	101	2125	9 + 18 27	10	204	102	102	2142
11-11 9	13	9 + 20 29	14	206	98	98	2098	10 + 23 33	1	217	109	109	2285
12-12 9	7	14 + 29 43	19	206	109	108	2232	15 + 29 44	8	211	114	113	2317
13-13 9	16	12 + 32 44	15	213	106	106	2230	12 + 32 44	1	227	115	115	2403
14-14 9	10	19 + 45 64	10	226	111	114	2386	17 + 40 57	11	230	118	118	2454
15-15 9	5	25 + 46 71	10	221	111	111	2327	20 + 43 63	7	222	115	115	2383
16-16 9	2	10 + 46 56	5	218	115	115	2367	7 + 38 45	0	227	120	120	2468

No.	Date	Thirteenth Day					Blood Sugar Mg./100 Cc. Fast. A.M. P.M.	Aver. Wt. Gain or Loss, Pounds	Ht., Inches	Wt., Pounds	Indura- tion %	Altro- phy %		
		From 0 to 12 Total	From 12 to 24 Total	From 24 to 36 Total	C.	P.								
		Cal.	Prots.	Fats.	Cal.	P.								
1	6 5	1	1	1	113	67	77	67	98	171	43	42 7	0	50
2	6 5	1	1	1	137	78	82	81	82	166	41	47	50	50
3	6 5	1	1	1	123	7	83	70	116	114	46 8	50 7	33	33
4	6 5	1	1	1	14	7	83	83	216	310	48	55	0	0
5	6 5	2	2	2	18	7	83	83	216	310	50 9	60 9	20	0
6	6 5	6	3	23	23	186	81	92	113	105	52 8	72 2	40	8
7	6 5	8	19	23	14	201	92	97	213	102	51 9	71 2	0	16
8	6 5	8	19	4	19	211	103	103	108	76	55 9	78 8	8	16
9	6 5	9	23	2	18	250	110	110	131	150	59 5	92 5	14	70
10	6 5	11	29	43	10	225	118	137	143	131	62 4	101 6	7	28
11	6 5	9	23	6	21	221	119	139	133	116	61 0	113 3	20	10
12	6 5	14	39	53	12	234	122	122	110	101	66 1	122	50	50
13	6 5	18	55	61	16	222	115	115	169	62	65 4	115	50	50
14	6 5	5	24	38	10	235	125	125	212	210				

The dietary formula followed is that established by the senior author¹ for juvenile cases of diabetes. The prescription for calories is based upon the age of the patient, namely 1000 calories at age one, and 100 calories added for each year of age until the completion of growth and development so that a child of ten, for example, would receive 1900 calories. The carbohydrate forms 40 per cent, the protein 20 per cent and the fat 40 per cent of the total calories. The diet for the boys increases until the age of 19, whereas the maximum diet for the girls is attained at the age of the completion of development at about 13 or 14 years. Protamine zinc and crystalline insulin were given as separate injections to each camper before the breakfast meal. The standard for control was (1) glycosuria in twenty-four hours to be less than 10 per cent of the carbohydrate intake and (2) freedom from diacetic acid or acetone.

The usual vacation period for each child was two weeks. This length of stay is adequate for the regulation of diabetes and allows for the maximum number of children to enjoy the advantages of the camp. Shorter periods of observation were due to homesickness. A few campers remained as long as two months which was the duration of the camp session. The boys' and girls' camps were run as entirely separate units, the former, Camp Tonawandah, in New London, New Hampshire, the latter, Clara Barton Homestead Camp, in North Oxford, Massachusetts.

On the day of arrival, the children were examined by the doctors, and insulin and dietary prescriptions, previously planned, were re-evaluated and changed as necessary. At least two local doctors were contacted in the vicinity of each camp to care for any immediate emergencies. If illnesses required hospitalization, the children were sent to the New England Deaconess Hospital in Boston.

The nurses, all of whom have had several years of training with diabetes, regulated the insulin according to the loss of sugar in the twenty-four hour specimens, and according to the single specimens voided at six, eleven, four and nine o'clock. The nurses treated reactions with supplementary carbohydrate, and occasionally in the moderately severe reactions gave 0.3 cc adrenalin hydrochloride (1:1000 solution) subcutaneously. They were also prepared to administer 50 per cent glucose intravenously if the occasion arose.

A summary of the boys' progress at camp is shown in Table I. There were eighty-six boys ranging in ages from 4 to 16 years. The table gives an average for each age group in regard to insulin requirement, number of grams of sugar lost in the twenty-four hours and the

dietary prescription for the first, sixth and thirteenth day of camp, the values for blood sugar taken usually on the same day at fasting, 11 00 A.M. and 4 00 P.M., the average weight, gain or loss, height, and the percentage of cases of insulin induration and atrophy.

The insulin requirements were generally slightly decreased or maintained at the same level. There was a sharp increase in the amount of insulin in the age groups from 12 years on. This corresponds to the onset of the development of the secondary sex characteristics and, in general, the insulin requirement increases with each succeeding year of age from an average of 17 to 63 units. The dietary prescription remained more or less constant during the two-week period for

TABLE 2

COMPARISON OF WEIGHT AND HEIGHT OF NORMAL AND DIABETIC BOYS

Age Years	Height, Inches		Weight, Pounds	
	Normal	Diabetic	Normal	Diabetic
5-5 9	41.5	41	41	47
6-6 9	43	47	46	51
7-7 9	45.5	48	48	55
8-8 9	48	51	59	61
9-9 9	51	53	62	72
10-10 9	52	55	69	71
11-11 9	55	56	77	79
12-12 9	56	60	85	93
13-13 9	58	62	99	102
14-14 9	59	64	114	114
15-15 9	61	66	121	122
16-16 9	64	65	122	115

the 4 to 7 year age groups but from 11 years on increases were necessary. The caloric prescription increased from 1523 calories for 4 year old boys to a maximum of 2565 for 16 year old boys. The carbohydrate increased from 143 for 4 year old boys to 235 gm. daily for those who were 16 years old.

The blood sugars reflected good control. For almost every age group there was a gain in weight noted during the two-week period. The heights and weights are compared with average heights and weights of normal nondiabetic boys in Table 2. This confirms previous observations that the diabetic has a wider range for height and weight than does the normal.

Induration at the site of injection of insulin was present in varying

TABLE 3
SUMMARY OF TREATMENT OF DIABETES—GIRLS

Age, Years	No	First Day					Sixth Day						
		Insulin, Units Prot. Zinc Total	Gm Glucose in 2½ Hours	C Gm	P Gm	F Gm	Calories	Insulin, Units Prot. Zinc Total	Gm Glucose in 2½ Hours	C Gm	P Gm	F Gm	Calories
4-4 9	3	9 + 9 18	16	145	64	72	1484	12 + 42 24	5	156	66	73	1545
5-5 9	2	7 + 44 21	6	163	78	81	1693	10 + 46 26	9	163	78	81	1693
6-6 9	4	5 + 40 15	12	157	71	76	1596	8 + 44 22	2	160	75	79	1651
7-7 9	2	9 + 45 24	17	160	79	82	1694	9 + 46 25	13	168	79	82	1726
8-8 9	7	11 + 46 27	4	171	82	87	1795	11 + 46 27	7	177	83	89	1841
9-9 9	11	11 + 20 31	11	186	86	92	1916	12 + 20 32	9	187	87	93	1933
10-10 9	8	10 + 49 29	10	180	85	88	1852	13 + 21 34	4	180	87	90	1878
11-11 9	10	10 + 30 40	20	192	89	91	1943	12 + 32 44	8	197	91	93	1989
12-12 9	12	18 + 34 52	13	191	94	95	1995	19 + 37 56	5	202	95	97	2061
13-13 9	12	20 + 41 61	17	198	96	97	2019	21 + 43 64	6	206	102	101	2141
14-14 9	18	20 + 36 56	22	204	98	99	2099	20 + 40 60	9	208	101	97	2109
15-15 9	12	25 + 41 66	10	199	92	92	1992	24 + 43 67	7	199	92	86	1938
16-16 9	7	19 + 60 79	18	196	92	91	1971	13 + 52 65	1	199	95	90	1986
17-17 9	6	25 + 49 74	14	189	93	95	1983	25 + 49 74	9	189	96	96	2004

Age, Years	Thirtieth Day					Blood Sugar Mg./100 Co. Fasting A.M. P.M.	Aver Wt. Gain or Loss, Pounds	Ht. Inches	Wt. Pounds	Indura- tion %	Atro- phy %
	Temp.	Food Total	Core Chlorine 10-15 hours	C. Gm.	P. Gm.						
6-8-9	3	11 + 15 26	6	177	68	71	1566	43.1	12	0	0
8-10-9	4	11 + 16 27	4	163	8	81	1693	41	42.5	0	0
10-6-9	6	8 + 11 22	3	161	76	79	1667	16	48	25	25
7-8-9	5	8 + 17 25	9	168	9	86	1762	47	48	0	100
8-8-9	5	11 + 15 26	7	172	81	90	1831	51	61	16	66
8-8-9	11	9 + 17 26	5	187	87	93	1923	51.6	69	9	36
10-10-9	8	13 + 1 23	13	183	87	90	1898	57	75	12	50
11-11-9	19	19 + 24 43	18	202	93	97	2061	58	80	10	50
12-1-9	12	16 + 35 52	6	201	101	103	2117	59	81	0	56
12-10-9	17	19 + 37 56	6	205	102	101	2169	61	97	33	25
14-10-9	16	9 + 37 52	4	208	100	97	2105	62.2	106	11	50
15-11-9	17	22 + 37 69	13	199	92	83	1929	61.8	119	25	42
16-10-9	7	15 + 51 66	2	193	97	78	1862	63.2	115	56	14
17-17-9	6	31 + 50 81	3	192	95	98	2030	61.5	111	17	50

percentages in the different age groups. A report by the senior author¹ shows that in 1939 only 10 per cent of all diabetic children had insulin pads or induration. Induration occurs less frequently with protamine

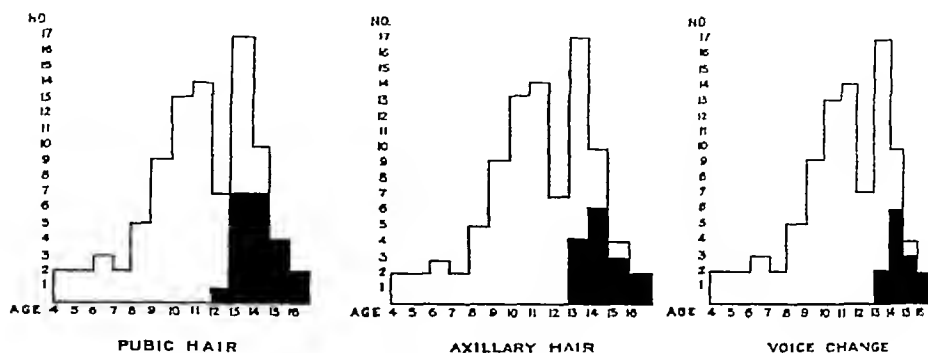


Fig. 55—Diabetic boys, development.

zinc insulin than with crystalline insulin. Variations in the site of injection of insulin decrease the number of pads. Nineteen per cent of the entire group of boys had induration. Local atrophy varied accord

TABLE 4
COMPARISON OF WEIGHT AND HEIGHT OF NORMAL AND DIABETIC GIRLS

Age, Years	Height, Inches		Weight, Pounds	
	Normal	Diabetic	Normal	Diabetic
5-5 9	41 5	44	45	42 5
6-6 9	43	46	48	48
7-7 9	46 5	47	50	48
8-8 9	47	51	59	61
9-9 9	49	55	70	69
10-10 9	51	57	78	75
11-11 9	53	58	83	80
12-12 9	56	59	88	84
13-13 9	57 5	61	99	97
14-14 9	60 5	62	104	106
15-15 9	61 5	62	106	119
16-16 9	62	63	116	115
17-17 9	62 5	62	110	114

ing to age, but appeared more prevalent at age 12 when 70 per cent showed it. Previous surveys indicate at least 30 per cent of the diabetic children have atrophy. This group of boys shows an over-all percentage of 23.

The sequence of secondary sex characteristics (growth of testes, pubic and axillary hair, change of voice, body hair and maturity) was recorded. Figure 55 illustrates the normal course of development of the diabetic boys. At age 12, there was only one patient with pubic hair. The 13 year old age group showed seven boys with pubic hair, six with axillary hair and two with change of voice. At 14, there were seven boys with pubic hair, six with axillary hair, and six with change of voice. At 15, all boys had pubic hair, three showed axillary hair,

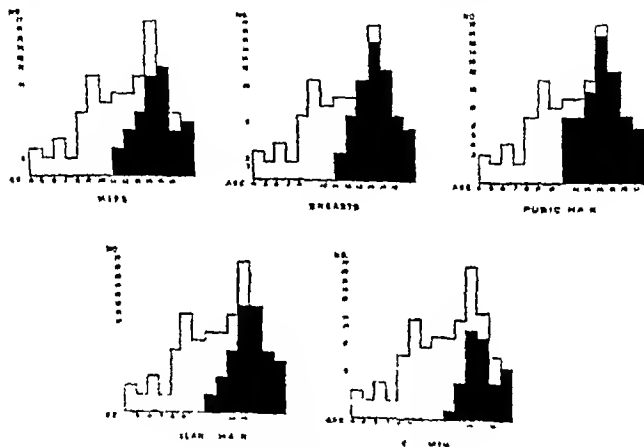


Fig. 55—Diabetic girls' development.

and three had change of voice. All boys of the 16 year old group showed pubic hair, axillary hair, and change of voice.

A summary of the 111 diabetic girls ranging in ages from 4 to 17 years is shown in Table 3. Generally the total calories were less for the girls than for the boys. The calories for the 4 year old girls were 1566 on the average and were increased to a maximum average of 2119 for 13 year old girls. The carbohydrate increased from 157 for 4 year old girls to a maximum average of 204 for 13 and 14 year old groups. The girls assume an adult calorie diet soon after the age of development because their growth is complete. The girls at ages 5, 14, 15 and 17 were slightly overweight for their height and age and they showed a weight loss in the two week period.

The blood sugars for the girls also showed good control. The insulin requirement remained more or less constant, indicating that, in general, the girls were in good control when they arrived at camp. Not a single group of the girls showed a loss of 10 per cent of their carbohydrate intake on the first day. Table 4 illustrates the weight-height relationships for this group of girls as compared with the normal for their age. Among this group of girls, 16 per cent showed induration at the site of the injection of insulin and 37 per cent exhibited some atrophy.

The normal course of development in the diabetic girls is shown in Figure 56. Development of hips, pubic and axillary hair and catamenia were recorded for each girl. By the fifteenth year, all the girls demonstrated the development of hips, breasts, pubic hair and axillary hair. The onset of catamenia was somewhat delayed, and was not complete in all girls until the 17 year age group.

The summer camp for diabetic children continues to be a valuable adjunct in the treatment of the disease and helps to combat the present shortage of hospital facilities.

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DIABETIC ACIDOSIS AND COMA

RANDALL G SPRAGUE, M.D., PH D (MED), F.A C.P *

LACK of control of severe diabetes may lead to diabetic acidosis, which is the forerunner of diabetic coma † The latter is a serious medical emergency which calls for prompt and energetic treatment based on sound physiologic principles if the life of the patient is to be saved

Fortunately, diabetic coma does not arise without ample warning Therefore, it can be averted if diabetic acidosis is either prevented or recognized early and treated effectively Usually, thirst and polyuria are present for a variable period of time before evidences of ketosis (acidosis) make their appearance Results of tests of the urine for glucose are strongly positive, and with the development of ketosis the results of tests for acetone and diacetic acid also become positive The early symptoms of ketosis are likely to be inconspicuous and deceptive Weakness, flushing of the face, headache, anorexia, nausea, pain in the legs, abdomen and back, shortness of breath on exertion and apathy are among the common early symptoms Later, all these symptoms are accentuated, and vomiting, dehydration, air hunger, somnolence and finally, coma, develop An appreciation of the grave potentialities of the early symptoms of acidosis should be had by every diabetic patient and his or her physician

ETIOLOGY AND PREVENTION

Diabetic coma may occur solely as a result of inadequate treatment of uncomplicated diabetes or, more commonly, as a consequence of a complicating condition which temporarily intensifies the diabetes Among elderly persons whose diabetes is mild coma does not occur

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† In some respects the term "diabetic coma" is misleading, for a patient may be gravely ill with diabetic acidosis without actually being comatose It has become our custom to apply the term "diabetic coma" to acidosis of sufficient severity to depress the carbon dioxide combining power of the plasma to 25 volumes or less per 100 cc. regardless of the state of consciousness of the patient Jones and his associates¹ limit the designation of "coma" to those instances in which the value is 20 volumes or less per 100 cc. of plasma on a titration of the patient's plasma

except in association with some complicating condition. When coma does occur, in old or young, it usually can be attributed to ignorance or neglect on the part of the patient (or the parents, if the victim is a child), the physician or both.

In most cases, the precipitating cause of acidosis and coma is one, or a combination of more than one, of the following factors: (1) omission of insulin, or the taking of insufficient amounts of insulin, (2) acute infection, particularly respiratory infection, (3) fracture of a bone, or other injury, (4) surgical operation, (5) hyperthyroidism, (6) pregnancy, and (rarely) (7) resistance to insulin. Dietary indiscretion, commonly believed to be an important cause of coma, is purposely omitted from the list. While this may be a factor in some cases, it is doubtful whether it is ever the sole cause. A careful history of the events leading up to the development of coma usually will disclose some other more important factor, such as an inadequate amount of insulin or intercurrent illness. Failure of the patient with severe diabetes to realize that he needs insulin, even if he is not taking food, is a particularly common error.

It follows from the foregoing remarks that diabetic acidosis of serious proportions usually can be prevented by careful day-by-day control of uncomplicated diabetes, and by adequate treatment of diabetes which is complicated by factors which tend to make it more severe than before. In the presence of intercurrent illness, the urine should be tested for sugar four times daily, that is, before each meal and at bedtime. If a grade 4 reaction with Benedict's solution is found, the Gerhardt test for diacetic acid should be performed. If glycosuria occurs in a case in which it was previously absent, or if the usual degree of glycosuria is found to be increased, but acetone bodies are not found, suitable adjustments of the doses of insulin can be made.

If, on the other hand, acetone bodies in addition to sugar are found in the urine, the situation is potentially more hazardous, and treatment must be pursued more vigorously. Some orderly procedure for the management of diabetes under such circumstances should be followed. Essential features of such a procedure are (1) frequent tests of the urine for sugar and acetone bodies, (2) administration of soluble insulin at frequent intervals in doses determined by the results of urine tests, and (3) maintenance of stores of glycogen (because they insure against ketosis) by the use of a simple diet which is fairly high in carbohydrate.

A simple and effective plan, based on suggestions by Woodyatt,⁸ is as follows. The day is divided into four periods of six hours each.

At the end of each six hour period the patient's bladder is emptied and the urine is tested for sugar and diacetic acid. Immediately after the test of the urine is completed a dose of soluble insulin is administered and a standard feeding which has a glucoso value of approximately 30 gm is given. This standard feeding may consist of 300 gm of orange juice, 300 gm of ginger ale, 400 gm of milk or any desired feeding which has a glucoso value of 30 gm. If the patient has not previously been taking insulin, the initial dose may be approximately 10 units. If he has been taking insulin, the initial dose may be a fourth or more of the total dose used in the previous twenty-four hours. If the patient has been using protamine zinc insulin or a combination of protamine zinc insulin and regular insulin, the usual dose may be administered at the beginning of the first six hour period of each day, in addition to the supplementary dose of soluble insulin, but in a separate site. If, at the end of the first six hour period, the urine still contains both sugar and diacetic acid, the dose of insulin for the second period is made 4 to 8 units more than that which was administered for the first period. Subsequent doses are increased if diacetic acid persists, left unchanged if glycosuria of grade 3 or 4 is present without diacetic acid, and reduced by 4 to 8 units if glycosuria of grade 2 or less is present. When the urine has been free of sugar, or nearly so, for two or three successive periods and the illness which precipitated acidosis has subsided, the previous program of treatment may be resumed.

In an occasional case in which the intercurrent illness has a profound aggravating effect on the diabetes, it may be advisable to modify the foregoing emergency program in the early periods by testing of the urine and the administration of soluble insulin at intervals of three hours. The standard feedings can be kept spaced six hours apart. If acidosis which is severe enough to produce symptoms is present, treatment should be carried out along the lines outlined below for diabetic coma.

PATHOLOGIC PHYSIOLOGY

With the development of severe diabetic acidosis almost all ingested carbohydrate is excreted in the urine in the form of glucose. In addition, virtually all sugar derived from ingested or body protein is lost in the urine. As a result, accelerated catabolism of fat and protein occurs in an effort to meet the energy requirements of the body. Sooner or later, the rate of formation of acetone bodies (acetone, beta-hydroxybutyric acid and diacetic acid) exceeds the rate of their

utilization in the tissues, so that they accumulate in the body fluids and are excreted in the urine and expired air. A state of diabetic acidosis then exists.

As a result of the foregoing events, serious secondary disturbances of fluid and electrolyte economy ensue. These disturbances may be factors of major importance in the production of coma and a fatal outcome. The passage of large amounts of sugar, ketone bodies, nitrogenous products and electrolytes into the urine provokes the excretion of tremendous quantities of water. Vomiting may further augment the loss of fluids and electrolytes. The result is a marked contraction of the volume of the extracellular fluid, including the blood plasma and, ultimately, loss of intracellular fluid as well. Severe dehydration may lead to renal insufficiency, anuria and circulatory collapse.

Before ketone acids are excreted in the urine they are neutralized by basic substances. At first, ammonia serves this purpose, but in severe ketosis the rate of formation of the ketone acids is so rapid that the ammonia mechanism is soon overwhelmed. Furthermore, with the development of renal insufficiency, the ability of the kidneys to produce ammonia is impaired. There is then a continuous loss of sodium and other basic ions in the urine. An additional part of the body's reserve of base is combined in the body fluids with retained ketone acids, other inorganic acids, phosphates and sulfates, at the expense of bicarbonate. At the same time there is a loss of chlorides in the urine and, in some cases, by vomiting.

The foregoing disturbances are reflected in profound alterations of the acid-base equilibrium of the blood plasma and extracellular fluid. The precise pattern of these alterations varies somewhat, depending on the severity and duration of the acidosis, the presence or absence of vomiting and the status of renal function. Three representative examples are given in *B*, *C* and *D* of Figure 57, together with, in *A* of the same figure, a chart of the normal acid-base equilibrium. A common feature of all instances of untreated diabetic acidosis is a reduction in the carbon dioxide combining power of the blood plasma. This is an indirect measure of the amount of sodium which has been lost through the kidneys plus the amount which is held in combination with acid substances in the body fluids. There is always more or less accumulation of ketone acids in the blood. The behavior of the plasma chlorides is variable and seemingly erratic. When acidosis is of long duration or is associated with vomiting, the plasma chlorides are likely to be decreased. Frequently, there is an accumulation of nitrogenous compounds in the blood because of accelerated catabolism of

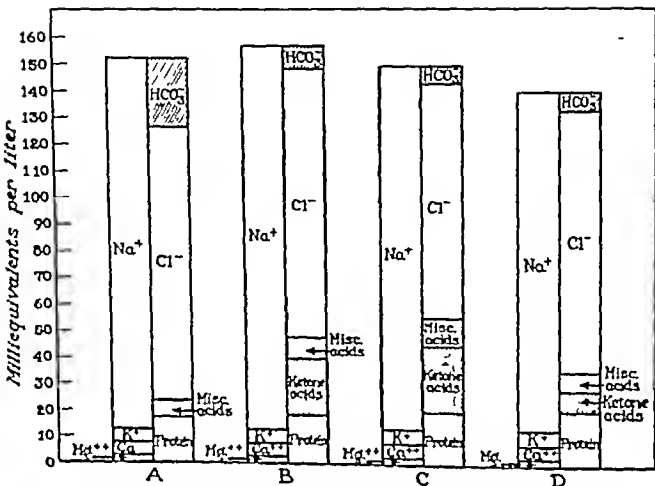


Fig 57—The acid base composition of the blood plasma in three cases of diabetic acidosis compared with normal. The data are charted after the method of Gamble. Values are expressed as milli-equivalents per liter of plasma. *Miscellaneous acids* include sulfates, phosphates, lactic acid, uric acid and amino acids. A is the normal pattern. B represents diabetic acidosis of a few hours duration in a girl 14 years old. Probably as a consequence of rapid dehydration, there has been a slight increase in the concentration of the total base of the plasma. There has been a marked reduction of the plasma bicarbonate roughly corresponding to the accumulation of ketone acids in the blood. The carbon dioxide combining power of the plasma is 14 volumes per 100 cc. The patient has vomited only once and the concentration of plasma chlorides has remained essentially normal. C represents severe diabetic acidosis of at least three days duration associated with vomiting in a boy 17 years old. Several factors have contributed to the reduction of plasma bicarbonate to a dangerously low level (plasma carbon dioxide combining power 14.7 volumes per 100 cc.) a large accumulation of ketone acids, a decrease of the total base and an increase of miscellaneous acids. The concentration of chlorides in the plasma has been reduced to 87 milli-equivalents per liter. D represents diabetic acidosis in a woman 50 years old who had been experiencing symptoms of uncontrolled diabetes for two years. Production and excretion of ketone acids probably had been in progress for a considerable period before she became critically ill. As a consequence there has been a marked decrease of the total base and a severe reduction of the plasma bicarbonate (plasma carbon dioxide combining power 17 volumes per 100 cc.) together with a relatively small accumulation of ketone acids in the blood. (Reprinted from Scrimgeour.)

tissue protein and impaired renal excretion. The concentration of total base in the blood plasma may be normal, increased or diminished, depending on the interplay of several factors, notably the relative rates of loss of water and of base. Until ketosis is far advanced, there is relatively little change in the reaction of the blood. Finally, however, all regulatory mechanisms fail and there is a progressive decrease in the alkalinity of the blood until it becomes slightly acid in reaction. Before the latter event occurs, coma usually has supervened and, indeed, death may have resulted.

Another feature of the disturbed electrolyte metabolism of diabetic coma which deserves more attention than it has received in the past is the loss of large amounts of potassium from the body. Thirteen years ago Atchley, Loeb, Richards, Benedict and Driscoll,¹ in a careful study of the metabolism of two diabetic patients, demonstrated a markedly negative balance for potassium as well as other basic ions during the development of diabetic acidosis, and a correspondingly large positive balance during recovery. Since most of the potassium of the body is in the intracellular fluid, it is within the realm of possibility that loss of potassium is responsible, in part, for the disturbances of function of the cells which lead to death in certain baffling instances of diabetic coma even, in some instances, after the electrolyte pattern of the blood plasma has been restored to normal. We have observed, for example, that in such cases the Kussmaul breathing tends to disappear, and a totally irregular type of respiration supervenes, suggesting a grave disturbance of function of the cells of the respiratory center or the muscles of respiration, or both. Holler⁴ recently reported an important case of diabetic coma in which, during the course of treatment, the value for serum potassium was reduced to an extremely low figure, with associated weakness of the extremities and of the muscles of respiration. Although the respiratory distress was so severe as to endanger life, prompt improvement and eventual recovery occurred after the intravenous administration of potassium chloride.

Clinically, the degree of depression of the carbon dioxide combining power of the blood plasma is a better measure of the severity of acid intoxication than is the degree of elevation of the blood sugar. Although the value for blood sugar usually is elevated, there is no reliable correlation between the degree of hyperglycemia and the severity of the acidosis. The degree of hyperpnea or air hunger, on the other hand, is approximately proportional to the depression of the carbon dioxide combining power, the degree of unconsciousness, however, may not be

TREATMENT

The victim of severe diabetic acidosis, with or without actual coma, is nearing the end of a rapid, downhill course. If he is to be saved, treatment must be initiated without delay and pursued energetically. *The prime essentials are prompt and continued administration of insulin in adequate doses and replacement of depleted reserves of water and electrolytes.*

Each patient in acidosis or coma presents an individual therapeutic problem. For example, a patient who has coma of long duration complicated by infection usually presents a more serious therapeutic problem than one who has uncomplicated coma of short duration. The administration of insulin, fluids and electrolytes cannot be reduced to fixed rules. Nevertheless, it is well to have in mind some basic principles of treatment which can be applied as necessary to meet the needs of the individual case. The response to treatment in the first three hours provides a clue concerning the vigor with which subsequent therapy must be pursued.

The patient in diabetic coma should be treated in a hospital, preferably by a team, the minimal personnel of which includes the attending physician, a laboratory technician and a capable nurse. They should be in constant attendance until the patient is out of danger. Inasmuch as prompt institution of treatment is an important factor in prognosis, administration of insulin should begin at home as soon as the diagnosis is made. If the journey to the hospital is a long one, additional insulin and even fluids can be administered parenterally en route. The hospital should be advised in advance when to expect the patient, so that arrangements for his care can be made.

Difficulties will be avoided if the course of treatment is subjected to careful laboratory control. To this end the values for blood sugar and plasma carbon dioxide combining power, and in some instances the blood urea and plasma chlorides, should be determined every three hours until the patient is out of danger. The results of these determinations, together with a running record of all treatment and notes concerning the clinical condition of the patient, should be charted in tabular form, so that a concise summary of therapy and progress is available at all times.

General Care.—The traditional treatment of diabetic coma calls for placing the patient in a warm bed, preferably in a private room, and conserving his body heat by means of warm blankets. However, results of experimental studies in recent years have suggested that the peripheral vasodilatation produced by heat may have a deleterious

effect in various shocklike states, and it is possible that these objections may apply with equal force to the use of heat in diabetic coma. Certainly, hot water bottles should not be used, for many patients have been burned by them. Gastric lavage with a 5 per cent solution of sodium bicarbonate is carried out.* This procedure often removes considerable material from the stomach, and aids in the detection of atony of the stomach. After the lavage has been completed, 300 cc. of the solution of sodium bicarbonate may be left in the stomach.

In the meantime, blood is drawn for chemical analysis, the patient is examined and an effort is made to determine why acidosis and coma developed. If the coma is not readily explained by omission of insulin or failure of the patient to take sufficient insulin, a careful search for some complication which might have precipitated the trouble should be made. Deserving of particular consideration are hyperthyroidism, respiratory infection, acute appendicitis, cholecystitis and infections of the urinary tract. If infection is found, appropriate measures for its treatment should be instituted, if possible.

The foregoing measures are adjuncts to the principal treatment. They should be carried out with speed and precision, and should not be allowed to divert attention from the prime essentials, namely, the administration of insulin, fluid and electrolytes.

Administration of Insulin.—If an adequate initial dose has not been given before the patient reaches the hospital, it should be administered within a few minutes after he arrives. Chief reliance is placed on soluble insulin. In addition, in some cases, the continuing effect of 50 to 100 units of protamine zinc insulin given at the outset of treatment has advantages.⁶ The size of the initial dose and of subsequent doses of soluble insulin must be gauged by the severity and duration of the acidosis, the age of the patient and the presence or absence of complications. In the presence of severe acidosis, the initial dose should be that amount which will give a maximal insulin effect as quickly as possible, that is, a dose which will produce as much effect as any dose. Woodyatt⁸ estimated that a dose of 2 units per kilogram of body weight will give a maximal effect, but at the Mayo Clinic we sometimes employ twice this amount. The insulin is injected subcutaneously in two or more sites to facilitate absorption. A second

* A liter of 5 per cent solution of sodium bicarbonate is prepared as follows. In 1000 cc. of cool, sterile, triple-distilled water dissolve 50 gm. of chemically pure sodium bicarbonate. The solution must not be boiled, for boiling would cause the formation of sodium carbonate. Half of the solution is used for gastric lavage and the other half is saved for intravenous administration, if this proves necessary.

"maximal" dose is administered in two to three hours and a third after a similar interval. When the condition is milder, and for small children, smaller doses usually are used.

The giving of a large total amount of insulin need not be a cause for concern, if the patient is observed carefully. Death in diabetic coma is much more likely to result from undertreatment than from overtreatment. The danger of a rapid transition from diabetic coma to hypoglycemic coma without warning symptoms is slight. Hypoglycemia is virtually unheard of in the first six hours of treatment of severe acidosis, even when tremendous doses of insulin are employed. If it occurs later it will not have serious consequences, if it is recognized and treated promptly.

When recovery becomes evident, the size of doses and frequency of administration of insulin can be diminished, depending on clinical judgment and the results of examinations of the blood and urine. For a time after correction of ketosis the diabetes continues to be more severe than previously, and relapses into coma may occur if adequate treatment is not maintained.

Fluids and Electrolytes—The patient in diabetic coma is always severely dehydrated. Restoration of hydration is essential for recovery. The most effective method in the early hours of treatment is the administration of isotonic solution of sodium chloride by venoclysis. The initial sample of blood for the determination of blood sugar, plasma carbon dioxide combining power, plasma chlorides and blood urea is drawn soon after the patient is admitted to the hospital, and administration of fluid is started at once without withdrawal of the needle from the vein. The first liter or two of fluid can be given rapidly, even when there is evidence of circulatory failure. For circulatory failure usually is due in large part to contraction of the volume of the circulating blood rather than to myocardial weakness. Subsequent intravenous injections may be given more slowly. Campbell, Reeser and Kepler² observed a patient with severe diabetic acidosis with coma to whom the administration of more than 9000 cc. of fluid in twenty-four hours was necessary for restoration of hydration and the formation of a relatively small volume of urine.

In a few cases there are rather clear indications for the judicious use of alkali. If the carbon dioxide combining power remains less than 15 volumes per 100 cc. of plasma while the blood sugar decreases markedly and distressing hyperpnea persists, 500 cc. of a 5 per cent solution of sodium bicarbonate may be administered intravenously slowly. Extreme hyperpnea usually can be quickly relieved by this

means * Recently, in some cases, we have employed a solution containing an excess of sodium ion from the outset of treatment in place of isotonic solution of sodium chloride This solution provides the patient with sodium and chloride ion in approximately the same relative concentrations as occur in the blood plasma In addition, the solution contains a small amount of potassium, which may offer some additional advantage in view of the loss of this substance from the body in diabetic acidosis. Although the use of such a solution seems to have a rational basis, sufficient data have not yet been accumulated to assay its usefulness in the treatment of diabetic coma †

As a rule, there is little to be gained by the intravenous administration of glucose during the first six hours of treatment, because the patient continues to excrete large amounts of unutilized glucose in the urine Later, when the blood sugar decreases and glycosuria diminishes, glucose can be administered intravenously, if the patient is not yet able to tolerate sweetened drinks by mouth

Treatment of Circulatory Collapse and Anuria.—These are grave prognostic signs which sometimes fail to respond to treatment. They are manifested by a falling blood pressure and a continued failure to form urine as hydration is restored. The initial treatment is the intravenous administration of adequate amounts of isotonic solution of sodium chloride Circulatory stimulants, such as digitalis and caffeine, are of questionable value The transfusion of whole blood or the infusion of blood plasma occasionally appears to be beneficial

PROGNOSIS

The prognosis depends largely on the duration and severity of acidosis, the age of the patient, the presence or absence of complications

* It should be pointed out that Joslin and his associates⁵ have established an enviable record in the treatment of diabetic coma without the use of alkali. However, there is little doubt that the administration of alkali hastens the restoration of normal acid-base balance in some cases, and occasionally may even be a deciding factor in recovery

† The solution which is being used at present was planned by Dr Alexander Leaf It is made up as follows to 700 cc of sterile isotonic solution of sodium chloride in a liter bottle are added 240 cc of triple-distilled water, 50 cc. of a molar solution of sodium lactate and 10 cc. of a 10 per cent solution of potassium chloride All solutions are kept in separate sterile containers, and are mixed just before the preparation is to be used. The final solution is slightly hypertonic, its composition in milli-equivalents per liter being as follows sodium, 158, potassium, 13, chloride, 123, lactate, 48 Additional clinical experience and the accumulation of more metabolic data can be expected to suggest some modification of the composition of this solution

and the promptness and adequacy of treatment. The fatality rate is higher among elderly patients than among young patients. Total unconsciousness, evidences of circulatory collapse, marked renal failure and the presence of overwhelming infection all are unfavorable signs. However poor the prognosis may appear at the outset, treatment should be pursued energetically, for not infrequently a patient who is practically moribund can be saved.

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TREATMENT OF DIABETIC COMA AND PRE-COMA

Coma Complicated by Bacteremia and Gangrene; Pre-Coma Associated with Lipemia Retinalis

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INTRODUCTION

THE complications accompanying various stages of diabetic coma and pre-coma vary in severity, in their effects upon treatment, and in their relationship to the pathologic physiology of the acidosis itself. Since the clinical features of diabetic acidosis change rapidly without clearly defined transitions from one stage to another, various classifications and indices of severity have been employed. It has been customary to classify cases of acidosis as true diabetic coma when the carbon dioxide content of the blood plasma is 20 volumes per cent (9 milli-equivalents per liter) or less. This is based upon the fact that in the period before the use of insulin patients with acidosis measured by a carbon dioxide content of blood plasma below 20 volumes per cent rarely recovered. It is recognized, however, that patients in the pre-coma stage of acidosis, when the blood carbon dioxide value may be between 20 and 35 volumes per cent, may have such serious complications that the prognosis is also critical. One of the patients here described entered in far-advanced diabetic coma with serious complications and the other in the pre-coma stage of ketosis with gross lipemia.

CASE I (Hosp. No. 7653) —A housewife, aged 67 years, with diabetes of eighteen years' duration, entered the New England Deaconess Hospital July 26, 1946 unconscious in diabetic coma. Her diabetic treatment had been begun in March, 1929 and she had taken insulin fairly regularly since that time. At her last examination on June 10, 1946 a barium enema had shown no filling defect but had demonstrated dense calcification of the iliac arteries as well as of the abdominal aorta. Coronary arteriosclerosis with angina of effort had been present for some years. An electrocardiogram in February, 1943

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showed regular rhythm, a QRS of 0.12 and P-R intervals of 0.12 seconds

The present illness had begun forty-eight hours previously with nausea and vomiting, for which reason she omitted her insulin. The dose had only been 12 units of regular insulin daily. She became unconscious soon and her local physician stated that she had been unconscious most of the day preceding admission.

The outstanding features of her examination upon admission were a rectal temperature of 101° F, pulse 120, blood pressure 80 mm of mercury systolic and 60 mm diastolic, acetone breath and Kussmaul respiration. The eyeballs were soft, the tongue and skin extremely dry but warm. No pulsation could be felt in the dorsalis pedis arteries. The abdomen was flat but rather tender. The presence of fever indicated clearly that some complications accompanied her acidosis and as is our custom the assistance of a surgical consultant was sought in order that no abdominal complications might be overlooked. Dr. Theodore C. Pratt noted the marked muscle spasm especially throughout the upper abdomen which was slightly greater on the right but still not sufficiently localized to justify a diagnosis of any surgical intra-abdominal disease. A blood culture was taken immediately and subsequently reported as showing a rich growth of *Escherichia coli*. Repetition of the blood culture on two occasions again showed positive growth of *E. coli*.

The blood specimen drawn immediately upon admission showed a blood sugar of 666 mg per 100 cc, plasma carbon dioxide content of 6 milli-equivalents per liter and a nonprotein nitrogen of 83 mg per 100 cc. She was immediately given 80 units of crystalline insulin subcutaneously which was repeated twice within the next two and a half hours so that she received 240 units within the first three hours after admission. Between 9:30 P.M. and 5 A.M. she received a total of 400 units with the result that the blood sugar had reached a normal value of 114 mg at 7 A.M., or nine and one half hours after admission. She was then able to speak but was obviously irrational.

Coarse rales could be heard at both bases and repeated vomiting made the administration of fluids by mouth quite impossible in spite of the fact that gastric lavage had been carried out promptly without obtaining any large amount of material. The x-ray examination of the chest was negative. The urine contained 96 mg of albumin and the sediment in a catheter specimen contained many pus cells. The fever, the persistent nausea and vomiting seemed due to an acute pyelonephritis. Examination of the blood had shown a surprisingly low white count of 6700 in contrast to the usual leukocytosis of diabetic coma. The red blood cells numbered 3,930,000 and the hemoglobin 12.500. The differential count was essentially normal. In Table 1 will be found a brief summary of her record.

Course—The bacteremia arising in the acute kidney infection was finally brought under control by the use of streptomycin, a million units a day for ten days. Blood cultures became negative. During the first week of her stay the patient received penicillin, 200,000 units daily. Her dietary treatment was difficult first because of the severity of the acidosis, secondly by reason of the infection and third because of a severe diarrhea. Explanation for the diarrhea was not clear although gastric analysis showed no free hydrochloric acid even after histamine injections. The diagnosis of pernicious anemia was naturally entertained but the red cells were not abnormally large. The mean corpuscular volume was 85, the determination having been made after dehydration was corrected.

TABLE 1

CASE I DIABETIC COMA COMPLICATED BY BACTEREMIA, PYELONEPHRITIS, POPLITEAL ARTERIAL THROMBOSIS, GANGRENE AND AMPUTATION OF LEG

Date 1946	Blood		Intravenous Fluids		Diet				Insulin, Units		Notes	
	Sugar Mg/ 100 Cc.	N P N, Mg/ 100 Cc.	Saline, Cc.	5% Glucose, Cc	C Gm.	P Gm	F Gm	Cal	Cryst.	Prot. Zinc		
July 26-27	666	83	2000	1500	75			300	400	0	0	Penicillin 240,000 units daily
27-28	114	55										
28-29	364			1000	109		38	436	74	8	16	Temp. 100.4° F
29-30	63											
30-31	143											
Aug. 10-11	256	38										
					121	50	63	1251			16	Streptomycin, 1,000,000 units daily for 10 days (Aug. 10-20)
13-14	203				139	59	73	1449		8	16	
14	Acute thrombosis, left popliteal artery				Amputation left thigh					16	40	
23-24	76				140	24	46	1070		8	36	
26-27	116											Weight 80 pounds.
Sept. 6	Discharged Urine		sugar free		149	67	82	1602	16 units daily			

The patient was given dilute hydrochloric acid by mouth. Her diet was concentrated by the avoidance of salads, coarse vegetables and raw fruits. She received vitamins in the form of vitamin B complex subcutaneously and thiamine by mouth. At one time three days after admission the abdomen became so distended that Wangensteen drainage was instituted for a short period. Liver extract was given, 15 units intramuscularly daily, as a means of controlling the diarrhea and also insuring a sufficient vitamin intake. In the diarrhea found in emaciated diabetic patients where no amebae or other infection is present liver extract has often been effective. The use of intravenous feeding using 5 per cent glucose solution in saline enriched with vitamins had to be continued because of her very limited intake by mouth. As will be

seen from the chart her total caloric intake often was as low as 700 calories and commonly between 1200 and 1400 calories.

On August 14, when it seemed that the kidney infection was coming under control, the patient suddenly developed pain in the left knee and lower leg which became cool and pale. An occlusion of the left popliteal artery was evident and emergency treatment was instituted. Low surface temperature and color changes from the midlower leg down to the toes were present but she still had motor power in the toes. The foot was kept exposed at room temperature. She was given papaverine, grain $\frac{1}{2}$, and niacine, grain 1, every four hours. The intermittent venous occlusion apparatus was used one hour on and one hour off day and night. Heparin was used twenty-four hours and followed by dicumarol which was continued for five days.

In spite of all these efforts the color of the foot steadily became worse until by August 20 it was evident that the blood supply was hopelessly deficient. During this time nausea and vomiting had become much more severe and the patient received intravenous administration of amigen solution. The prothrombin time fell as low as 51 per cent and at this level she had a rectal hemorrhage, requiring transfusion. Her general condition was not seriously affected and left thigh amputation was carried out on August 23. The operation was performed by Dr. Theodore C. Pratt under spinal anesthesia, no shock developed and her recovery during the next few days was rapid.

The patient was discharged with the stump entirely healed on September 6. At this time the urine was sugar-free and had been so for several days. The blood sugar was normal. The insulin dose had been rapidly reduced because of occasional low blood sugar values until she required only a single dose of 16 units of protamine zinc insulin daily. On November 9, 1946 she cheerfully displayed a healed stump and walked well with crutches.

Summary—After eighteen years of diabetes the development of acute pyelonephritis with bacteremia resulted in severe diabetic coma partly because of the omission of insulin upon advice that the nausea and vomiting which prevented the taking of food required the omission of insulin. The bacteremia was cured by means of streptomycin and penicillin after recovery from diabetic coma. A severe nutritional problem was present indicated by anemia of the secondary type which responded poorly to iron and other medication. The diarrhea was brought under control by means of liver extract and dietary adjustment. Sudden development of arterial thrombosis in the left leg and subsequent gangrene necessitated amputation of the leg, from which recovery was uneventful.

CASE II (Hosp No 29387) —A student 19 years of age entered the New England Deaconess Hospital September 3, 1946 because of drowsiness and fatigue. He had taken his usual dose of 40 units of protamine zinc insulin early that morning but because the urine contained 3.5 per cent sugar upon admission he was given 20 units at 9:30 P.M. The twelve hour urine specimen contained 4.9 per cent sugar, 4 plus diacetic acid, and the fasting blood sugar was 274 mg with a plasma carbon dioxide content of 13 millimols. The patient though somewhat drowsy upon admission was not vomiting and was not acutely ill.

The patient's diabetes had begun with the usual polyuria in January, 1945. His maximum weight was 165 pounds dressed in 1945 and his

TABLE 2

CASE II LIPEMIA RETINALIS AND DIABETIC ACIDOSIS IN A STUDENT, AGED 19 YEARS, WITH DIABETES OF EIGHTEEN MONTHS' DURATION

Date	Blood			Urine		B M R.	Diet				Insulin, Units		Thyroid Ext. Gm.	Weight Pounds
	Sugar, 100 Cc. Fasting	Choles. Mg./100 Cc.	CO ₂ , Mm. per Liter	Sugar 24 Hrs. Gm.	Acetone		C. Gm.	P Gm.	F Gm.	Cal.	Prot Zinc	Cryst.		
1946														
Sept. 3							63	26	31	655	40	20		
4	274		13	102	trace		162	85	105	1933	40	180		
5	230		21	101	0		165	83	102	1910	58	40		
6											100	60		
7	294	1590		66	0		200	90	105	2105	80	104		149
8		1610		99	0						60	144		148
10	241	1360		66	0		200	87	82	1856	120	124		149
11	422	1405		120	0		193	95	71	1811	120	172		149
14	225	1235		13	0						120	80		
17					0		252	104	71	2063	100	76		148
19	124	1190		0	0						100	60		148
21	163	1190		0	0	-33					100	76		146
23	204	865		0	0						100	70		
25				0	0	-31					100	70		145
27	165	845		0	0						100	70	0.2 G	
30	130	818		0	0	-16					100	70	0.2 G	
Oct. 4	111	795		0	0	-20	180	90	110	2070	100	70	0.3 G	146
Nov. 6	140	171		0	0	-7					90	60	0.3 G	147

In spite of the low basal metabolic rate and high blood cholesterol the patient's history did not suggest hypothyroidism. He had been unusually vigorous until the month preceding his acidosis. Indeed he had walked three miles a few days before admission. His appearance did not suggest hypothyroidism. He was muscular, lean, and after his dehydration was relieved his skin texture and tone were excellent. His hair was healthy and of normal distribution.

height 6 feet 1 inch. From January to November, 1945 he did well on diet alone but then polyuria returned and insulin was started. By December, 1945 he was taking 40 units daily and then was placed on a relatively high fat diet taking 2 pounds of bacon in a week and about 3 ounces of butter daily. He worked at college as a milk peddler and meals were irregular. He gave up work one month before admission because of exhaustion.

When his blood was drawn for chemical analysis it was observed to be light in color and upon separation the plasma was creamy white in appearance. An examination of the eyegrounds showed that arteries and veins had practically the same color, a salmon pink, the disks were normal, no hemorrhages or retinitis was evident. Lipemia retinalis was clearly evident and was confirmed by the report of the blood content of 1590 mg. of cholesterol. Because of his moderate acidosis insulin was given each hour during that day with the result that he received fifteen injections in amounts that varied from 4 units to 20 units according to the tests or a total of 180 units of crystalline insulin plus 40 units of protamine zinc insulin. During the next few days he continued to require large doses of insulin and the blood values for cholesterol continued to be high in accordance with Table 2.

Within a few days the color of the vessels changed and the gross lipemia disappeared. However, the patient did not become sugar-free for ten days and continued to show an extraordinary degree of insulin resistance. The x-ray examination of chest and legs for arteriosclerosis was negative. The electrocardiogram showed low T waves almost isoelectric in all leads, but with normal voltage in the ventricular complexes. Although the clinical features of myxedema were absent, he was given thyroid extract 0.3 gm. daily. No cause was found for the insulin resistance.

At discharge all urine specimens were sugar-free. His diet was carbohydrate 180 gm., protein 90 gm. and fat 110 gm., and his insulin dose was 100 units protamine zinc insulin and 70 units crystalline insulin.

Summary—A young man with diabetes of short duration presented gross lipemia retinalis associated with only moderate acidosis which developed after a period of some months on a high diet without adequate control of his diabetes with a sufficient dose of insulin. For the low basal metabolic rate of minus 33 per cent, he received thyroid extract 0.3 gm.

SYMPTOMS AND COURSE OF DIABETIC COMA

The character and severity of symptoms depend mainly on the degree of reduction in the alkaline reserve. Thus there may be marked ketonuria with a strongly positive reaction for acetone and diacetic acid with no symptoms whatever because as yet no real acidosis has developed and the carbon dioxide content of the blood is still normal. As the ketosis increases and a decline in the carbon dioxide content of the blood occurs, the following symptoms commonly may be observed

(1) weakness, (2) loss of appetite or nausea and vomiting, (3) flushed cheeks, (4) slightly increased frequency of respiration, (5) acetone odor of the breath, (6) slight drowsiness. Case II illustrates this early stage of acidosis but this case is unusual in that gross lipemia was present also.

With advancing acidosis, in addition to the preceding symptoms, abdominal pain, severe constipation and marked air hunger are frequently observed. As drowsiness advances there may come a stage in which the patient apparently responds normally to questions but actually the central nervous system is so much affected that after recovery he will have no recollection whatever of the conversation or even of such vigorous treatment as gastric lavage. Unconsciousness usually does not occur until the acidosis has reached such a level that the carbon dioxide content of the blood is below 9 millimols (20 volumes per cent), except in those cases in which a complicating infection or vascular lesion may render the brain more sensitive to milder degrees of acidosis. This is often the case in children, in whom an acute infection complicating acidosis or precipitating the acidosis may be followed by unconsciousness when the acidosis is at a level measured by a carbon dioxide content of the blood of perhaps 25 to 30 volumes per cent. Nausea and vomiting are almost always present in the history of a patient who has true diabetic coma. Yet exceptions exist. As this is written a young girl was admitted to the Deaconess Hospital with a blood carbon dioxide content of 5 millimols, and intense air hunger—typical diabetic coma. She was not unconscious and denied having nausea or vomiting, yet gastric lavage yielded 600 cc of thick food material mixed with tarry, black changed blood.

In full coma the urine shows much glucose, diacetic acid and acetone until the stage of exhaustion comes on when, with failing kidney and liver function, the amount of sugar in the urine declines and acetone bodies may even disappear. The typical coma shower of short granular casts almost filling the field should always be sought. The microscopic examination may show pyuria as in Case I in which a severe complicating infection of the genitourinary tract underlies or complicates coma.

Physical examination in advanced coma reveals a blood pressure far below normal, rapid pulse, rapid deep respiration and evidences of dehydration. Thus the eyeballs are soft to the touch, the skin is cold and the extremities mottled. Sometimes a distended stomach can be seen filling the epigastrium. The bladder is often full and distended.

because of beginning paralysis. The white blood count is usually elevated to values from 25,000 to 50,000 although, when severe infection is present, depression of the bone marrow may alter the blood cytology.

In Case I an infection developed in the genitourinary tract which caused the nausea and vomiting. Then insulin was omitted and severe acidosis rapidly progressed. Possibly bacteremia resulted from the breakdown in the natural defenses consequent upon the subsequent acidosis and dehydration. It is a most serious decision to advise any diabetic patient to give up insulin and insulin should never be omitted unless blood and urine tests clearly indicate it.

PATHOLOGIC PHYSIOLOGY OF COMA

It has long been accepted that the three acetone bodies, beta, hydroxybutyric acid, diacetic acid and acetone are found only in traces in the blood and urine of normal individuals on normal diets but they may increase in amount during starvation or periods when the carbohydrate of the diet is greatly restricted. The formation of these ketone bodies occurs chiefly and almost entirely in the liver by a breakdown of fatty acids. These ketone substances are oxidized chiefly in the muscles and it is generally believed that diabetic muscles can oxidize these substances as well as normal muscles. Their accumulation in a patient with uncontrolled diabetes is due to a rate of formation which exceeds the capacity of the tissues for utilization.

The various chemical steps by which they are produced has been the subject of much study. The older Knoop theory is now generally discredited and at present the beta-oxidation-acetic acid condensation hypothesis of MacKay is accepted. The body is able to adapt itself to a certain increase in the content of acetone bodies partly by excretion in a highly acid urine and partly by neutralization and excretion as ammonia salt. Furthermore, carbon dioxide is displaced from the bicarbonate of the plasma by the ketone acid, and by means of this buffer action and also that of the blood protein considerable amounts of ketones can be taken up without appreciable change in the blood. When, however, excessive amounts accumulate and hyperglycemia is present, urinary excretion results in great loss of base, chiefly sodium. Increased excretion of water brings about dehydration. The result is a lower body fluid volume and a lowered concentration of base.

Particular importance at present is assigned to the loss of potassium although the loss of sodium in acidosis is known to be much greater in amount. In severe acidosis the loss of potassium from the cells may itself be the most important factor in the cellular depletion and pos-

sibly the cause of death in complicated coma. A striking instance of deficiency in serum potassium is reported by Holler.¹ A girl aged 18 years was admitted in coma with a blood sugar of 400 mg. She was given an excessive amount of glucose solution in isotonic solution of three chlorides and an excessive diuresis of 15,325 cc of urine was produced. She developed respiratory paralysis and was found to have a low serum potassium value of 2.5 milliequivalents per liter. When the blood potassium was raised by intravenous injection, she made a recovery.

In addition to the loss of base in the urine body chloride may be depleted in part by the vomiting and in part through the urine. In certain cases, therefore, the blood chloride is reduced and anuria is relieved only by giving hypertonic chloride solution by vein.

The objectives in treatment of coma are summarized by Joslin, Root, White, Marble, and Bailey² as follows: "It has long been held that the utilization of carbohydrate exerts an antiketogenic effect and the primary aim in treatment of diabetic coma is to improve the oxidation of glucose. Woodyatt held that the oxidation of sugar not only spared the oxidation of fatty acids but had an additional antiketogenic effect. Stadie emphasizes total magnitude of the fat metabolism and regards the metabolism of 2.5 grams fat per kilogram as the upper limit, beyond which ketosis will occur. Mirsky and Soskin regard the presence of glycogen in the liver as the essential condition to avoid ketosis. It should be noted that coma patients can die with livers well supplied with glycogen. Probably in the well treated coma case both an increase in glucose oxidation and an increase in glycogen storage occur."

LIPEMIA

Diabetes is the only disease in which lipemia is frequent enough to have special importance. It is true, however, that the number of diabetic patients whose blood shows an abnormal concentration of lipids today is decidedly less than was true twenty or thirty years ago before the use of insulin. Thus in the years 1916 and 1917³ the average cholesterol values for 167 patients were 385 mg for the first group of 131 cases and 360 mg for thirty-six adults in the year 1916. These average values declined steadily in subsequent series. At present lipemia is rarely found in diabetic patients.

The origin of the fat in diabetic lipemia appears to be mainly the fat of the food. The patient in Case II had lived on a high fat diet with evidently insufficient insulin to provide a proper metabolism of carbohydrate. However, another factor in his case was the low basal

aorta and the aortic arch. The transition to the thoracic aorta is sharply angular (Fig 74)

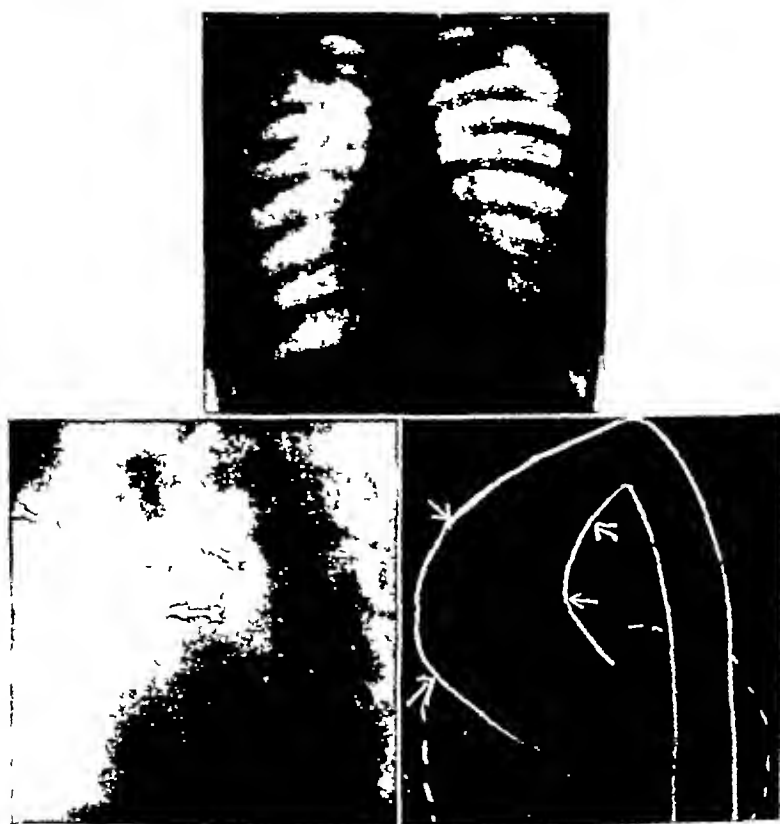


Fig 74 (Case V)—Aortic stenosis, anomaly of aorta. The ascending aorta is markedly dilated. The isthmus shows a sharply angular deformity.

Case VI Aortic Stenosis Coarctation of the Aorta

T W is a boy of 5. The patient's birth and early development has been perfectly normal. There is no history of cyanosis, dyspnea, etc. In February, 1946, he contracted measles at which time his physician discovered a loud systolic murmur over the aortic area. The parents had never been told previously that the child had a murmur.

Physical examination reveals a well developed boy of healthy complexion. There is no apparent cardiac enlargement. An intense systolic thrill is felt over the aortic area and over the arteries of the neck. The pulsations in the lower extremities, femoral, popliteal, posterior tibial and dorsalis pedis, are felt with the greatest difficulty. On the other hand, faint but definite arterial pulsations are felt over both scapulae and upper intercostal spaces posteriorly. A loud, coarse systolic murmur is best heard over the aortic area and over the carotid arteries. The second aortic sound is of normal intensity. These auscultatory findings are

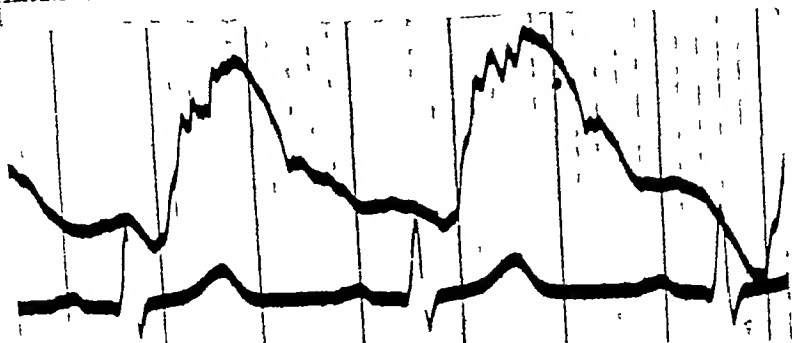
metabolic rate of minus 33 per cent, which was not associated, however, with clinical evidences of myxedema. Until acidosis developed he had been vigorous and strong, and after its relief the skin, the face and his general appearance again in no way suggested myxedema. Occasionally postoperative myxedema results in an increase in blood fat and lipemia with typical xanthomatosis as occurred in the palms of a diabetic housewife whose metabolism fell to minus 30 per cent following thyroidectomy. Relief is quickly obtained in such cases by treatment with thyroid extract. Lipemia has occurred in association with diabetic coma or diabetic acidosis in three other cases at the Deaconess Hospital and in seven cases among 108 cases of diabetic coma reported by Baker.⁴ It is not uncommon to have increases in the blood cholesterol and blood lipids to a moderate degree but true lipemia is still rare.

Lipemia retinalis such as was observed in Case II has been noted in eleven other instances at the Deaconess Hospital, including the two cases reported by Gray and Root. The ages of these patients varied from 21 to 40 years. The complication has occurred most commonly in young diabetic patients, frequently males, often with mild degrees of acidosis. It has been noted that the characteristic salmon color of the veins and arteries in the eyes reverts to normal when the blood fat concentration falls to 5 per cent or less. It is the fat of the blood which falls rapidly under treatment, whereas the cholesterol decreases slowly. Formerly this complication of the diabetes was regarded as hopelessly fatal but since the use of insulin it has rarely had a serious prognosis.

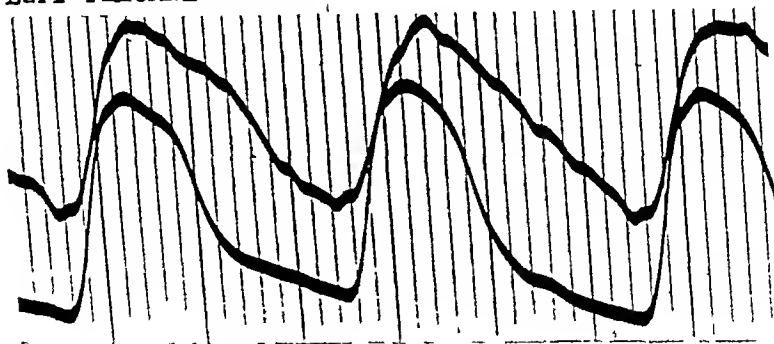
Lawrence⁵ describes an extraordinary lipemia in a woman aged 26, who presented at her first examination xanthomatosis involving the arm, knees and neck. Her diabetes proved to be extraordinarily resistant. The blood cholesterol was 417 mg per 100 cc and the total fat was 6 volumes per cent. She had a large liver and spleen which slowly increased in size. Over a period of seven years' observation she developed a complete lipodystrophy with a disappearance of all fat tissues. The intense lipemia continued and was lowered only when the high blood sugar level was reduced to normal by large doses of insulin. Her metabolic rate was constantly elevated and at times reached the level of plus 150 per cent. The maximum amount of insulin required was 2000 units daily. Thyroidectomy reduced the basal metabolism to plus 40 per cent and then myxedema developed. A complete postmortem examination showed fatty enlargement of the

confirmed by phonocardiographic examination Arterial pulse tracings recorded over the carotid arteries show an anacrotic notch, systolic plateau and systolic vibrations (Fig 75) Simultaneous pulse tracings recorded over left radial and

ARTERIAL PULSE LEFT COMMON CAROTID



LEFT FEMORAL ARTERY



LEFT RADIAL ARTERY

Fig 75 (Case VI) —Aortic stenosis, coarctation of the aorta The anacrotic notch, the slow rise, systolic vibrations and plateau recorded in the arterial pulse tracing indicate obstruction to the left ventricular outflow tract (aortic or subaortic stenosis) Simultaneously recorded left radial and left femoral arterial pulse tracings reveal the radial pulse precedes the femoral pulse by 0.03 seconds This is characteristically found in coarctation of the aorta

left femoral arteries reveal the radial pulse to precede the femoral pulse by 0.03 seconds (Normally, the femoral pulse precedes the radial pulse 0.04 to 0.08 seconds [Fig 75]) Blood pressure readings were 112/68 in the left arm and 114/72



Fig 76 (Case VI) —The conventional roentgenogram reveals an increased rounding of the left ventricular contour. The double contour to the right is thought to be due to a persistently enlarged thymus. The angiocardigram reveals considerable dilatation of the ascending aorta, markedly narrowed aortic arch isthmus and proximal segment of thoracic aorta. A moderate dilatation of the aorta beyond the stenosis can be seen. The internal mammary artery is well visualized and is of increased caliber.

in the right arm. The blood pressure in the legs was 80 to 85 mm of mercury systolic and 60 to 65 mm diastolic.

The only positive electrocardiographic finding is high voltage of QRS complexes in the precordial leads.

Fluoroscopic and conventional roentgenographic examination reveals an increased rounding of the left ventricular contour. A double contour is seen to the right of the spine in the supracardiac area, probably due to a persistently enlarged thymus (Fig 76).

Angiocardiographic examination reveals a moderate enlargement of the left ventricle. The ascending aorta is considerably dilated. The aortic arch, isthmus and the transitional segment of the thoracic aorta are markedly narrowed. The poststenotic segment is moderately dilated. The internal mammary artery is well visualized and of increased caliber (Fig 76).

CONCLUSIONS

1 The diagnosis of aortic or subaortic stenosis should be considered whenever a loud, harsh systolic murmur is encountered in the right second space, over the mid sternum or at Erb's point. The presence of a soft diastolic murmur without peripheral signs of insufficiency does not contradict the diagnosis.

2 The arterial pulses, both by palpation and through recordings afford the most important single diagnostic criterion for the diagnosis.

3 There is no pathognomonic method for differentiating aortic and subaortic stenosis.

4 Dilatation of the ascending aorta beyond the stenotic segment is common.

5 Associated anomalies of the aorta are frequent. Isthmic narrowing and angulation may be found. Frank coarctation is not uncommon and if marked may be proven by demonstrating a delay in the femoral pulse wave as compared with the radial and by angiocardiography.

6 Aortic and subaortic stenosis are not as commonly benign as is ordinarily thought.

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Fig 76 (Case VI) —The conventional roentgenogram reveals an increased rounding of the left ventricular contour. The double contour to the right is thought to be due to a persistently enlarged thymus. The angiogram reveals considerable dilatation of the ascending aorta, markedly narrowed aortic arch isthmus and proximal segment of thoracic aorta. A moderate dilatation of the aorta beyond the stenosis can be seen. The internal mammary artery is well visualized and is of increased caliber.

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THE TREATMENT OF ACUTE RHEUMATIC FEVER AND ACUTE RHEUMATIC HEART DISEASE IN CHILDREN

LEO M. TARAN, M.D.*

THE treatment of acute rheumatic fever and rheumatic heart disease has received less attention in medical literature than the study of the epidemiology and pathogenesis of the disease. This may be due to the fact that the evasive and ill-defined manifestations of rheumatic fever failed to bring forth clear-cut evidence to satisfy the of the disease from the standpoint of therapy. It must be admitted that, to date, bedside and laboratory investigation in the field of rheumatic fever failed to bring forth clear-cut evidence to satisfy the criteria of an infection, an allergic state, a disturbance in endocrine economy, or a genetic maladjustment. On the clinical side, the disease has not been unhesitatingly placed among the acute toxic illnesses or chronic protracted diseases running a natural and unalterable course. Furthermore, many attempts at symptomatic therapeutics apparently failed to modify the course of the disease.

This background in the evolution of the understanding of rheumatic disease helped to discourage the most ardent student of rheumatic fever from pursuing the search for therapeutic means of combating this illness. As a result, two schools of thought have grown up with regard to the treatment of rheumatic fever. There are those who are of the opinion that all energy and resources should be devoted to the study of the cause of rheumatic disease. These feel that a specific therapy might follow once the etiology is known. A second and much smaller group of students of rheumatic fever believe that the disease and its sequelae might be significantly modified in favor of the patient by a rational therapy directed against the major and minor manifestations of the disease.

CONCEPTS OF AN ADEQUATE THERAPEUTIC REGIMEN

Many years of detailed and well documented experience with statistically significant numbers of rheumatic children presents solid evidence to show that the treatment of acute rheumatic fever and rheumatic heart disease can and does favorably influence the outlook

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for the rheumatic child.* These favorable results attained with rheumatic children stem from a therapeutic regimen which is predicated upon the following concepts:

1 Rheumatic fever is an acute toxic disease of many months or years duration

2 It is universal in its attack upon the human organism, but always and most damagingly invades the cardiac structure and function

3 It is, in our opinion, not a chronic illness, but rather an acute process whose manifestations are at times explosive and even ful-

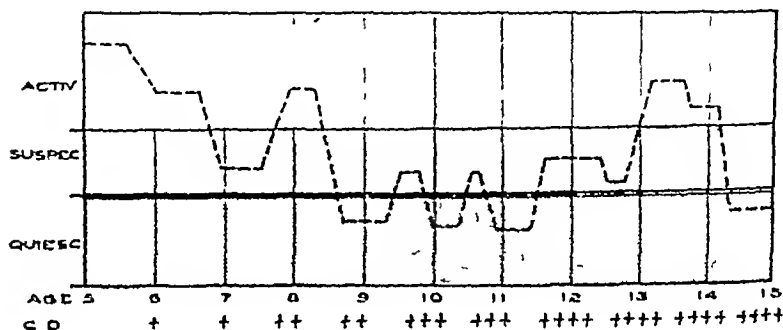


Fig 77—This chart represents the course of rheumatic activity over a period of ten years in a patient who came under observation at 5 years of age with an attack of rheumatic polyarthritis. It is noteworthy that during the period of so-called quiescence she had many symptoms of rheumatic disease, i.e., joint pains, occasional epistaxis and the like without manifest exudative episodes. During this period, cardiac dilatation and hypertrophy continued unabated. She has had a total of three "explosive" phases, but continued, in our opinion, to be mildly active when judged by changes in cardiac status.

minating, and at other times smoldering but none the less progressively damaging, at times the disease is subclinically active but continuous and eventually lethal in its effects, and at still other times mild and impalpably active but self-limited and with few sequelae. The dominant feature in all these manifestations, however, is that the disease is continuous and fluctuates in type and degree of clinical behavior rather than that it is repetitive and subject to recurrences (Fig 77). Our experience with rheumatic children seems to postulate that rheumatic fever when it reaches the stage of clinical recognition is in the vast majority of instances a manifestation of a reactivation

* An opportunity for this experience was presented at the St. Francis Sanatorium for Cardiac Children where rheumatic patients are treated and observed over many months and often years. One hundred and fifty boys and girls, 6 to 16 years of age, are treated for an average of twelve months, more than one half of this number have been studied carefully for many years after discharge from the sanatorium.

of an existing active process rather than a recurrence engrafted upon a "quiescent" state

4 In the present state of our knowledge, the most permanent crippling effects of the disease are demonstrated in disturbances of cardiac function, the degree of functional cardiac disability, in our experience, is in most cases a manifestation of the severity of the active process in the heart muscle and not a measure of the extent of valvular damage. In addition, it is apparent from our observations that cardiac disability in rheumatic disease is in most instances encouraged by failure to place the heart at physiological rest during the acute inflammatory process

5 Treatment which alters the manifestations of the explosive phase of the disease clearly and favorably modifies the outcome of the disease. Adequate management and care during the active phase of rheumatic fever may not only shorten the duration of the disease and minimize its inroads upon the heart, but also, in our opinion, prevent reactivations or recrudescences

It is the thesis of this paper to present an experience with the treatment of acute rheumatic disease in children who were managed on a therapeutic regimen which adheres to the concepts presented above. This paper is limited to the discussion of the treatment of the acute phase of the disease. The prevention of rheumatic fever, its onsets and recurrences will not be dealt with here

CLASSIFICATION OF RHEUMATIC FEVER

For many years we have classified rheumatic fever into four distinct phases from the therapeutic standpoint (1) the latent or preparatory phase during which the patient has rheumatic symptoms of a mild nature but does not present classical manifestations of the disease, (2) the "explosive" phase of rheumatic fever during which the patient presents the acute phase of the major manifestations of the disease, (3) the protracted phase during which the patient continues to have both clinical and laboratory evidence of rheumatic fever but is not acutely ill and does not manifest acute cardiac disease, (4) the phase of acute rheumatic fever with manifest heart disease during which the patient has acute heart failure

LATENT PHASE OF RHEUMATIC FEVER

It must be admitted that this phase of the disease, in our experience, is most refractory to therapy. Measures to improve the nutritional state of the individual, correction of the emotional and physical environment under which the patient lives, removal of foci of infection such as tonsils, adenoids and carious teeth, removal of the patient to a subtropical climate, a high vitamin intake, chemotherapeutic measures for preventing upper respiratory infections, small and large doses of

salicylates given over long periods of time—all these therapeutic measures were attempted in significant numbers of cases, but failed to prevent the explosive phase of rheumatic fever. It remains to be seen, however, whether acute rheumatic attacks in a patient who already has latent rheumatic disease could be prevented with the newer chemotherapeutic agents.

EXPLOSIVE PHASE OF RHEUMATIC FEVER

1. ARTHRITIC AND VISCERAL MANIFESTATIONS

The acute explosive or exudative phase of rheumatic fever may be universal in its anatomical distribution or may be clearly demonstrative in certain distinct and circumscribed areas. While joint manifestations in the form of migratory polyarthritis are common, this form of rheumatic manifestation rarely occurs as the only manifestation of the disease. In acute polyarthritis, other manifestations are often in the subclinical background and not easily detected. Visceral manifestations—pericarditis, pancarditis, pneumonitis, pleuritis, peritonitis, arteritis, nephritis and the like—are widespread in distribution but always with a predilection and emphasis, in the individual patient, upon a certain specific structure. The point to be stressed is that whatever form the explosive phase of the disease takes, the treatment must be directed toward limiting the exudative process rather than toward the treatment of the organ or set of organs involved. To limit the early exudative process salicylate therapy, in our experience, is the treatment of choice.

Massive Doses of Salicylates.—The specificity of salicylates as a therapeutic agent in rheumatic disease has been called into question on numerous occasions during the past fifty years. Many years back, large doses of salicylates were used in polyarthritis and acute pericarditis, often with startling results. The confusion raised by the occasional untoward effects of salicylates and their apparent impotence in preventing cardiac damage discouraged their use. The recent observation of Coburn¹ that adequate salicylate therapy may modify "the sterile inflammatory reaction which occurs during the activity of the rheumatic process," and thus "inhibits the development of cardiac disease" has once again reawakened the question of specificity of salicylates in the treatment of rheumatic disease. A number of communications which appeared in the literature before and since the statement of Coburn have attempted to deny his contention and some demonstrated the apparent salutary effects of salicylate therapy in some phases of rheumatic disease, but these refused to subscribe to the specificity of its effects.^{2 3 4 5 6 7 8 9 10}

A careful review of these polemics on the good, indifferent and bad effects of salicylate therapy in rheumatic fever fails to point up a clearly defined area of disagreement. Adequate salicylate therapy, in our opinion, is a specific treatment for a specifically defined manifesta-

liver and portal cirrhosis with an extraordinary enlargement of the lymphatic glands Lawrence suggests that the lipo-atrophy produced the increases in blood sugar and fat by preventing the important action of insulin in changing sugar into stored fat so that both substances circulated in excess This important aspect of insulin action is sometimes forgotten, especially in considering the use of large amounts of glucose in diabetic acidosis

A striking difference occurs between the lipemia of diabetes and the increased cholesterol value seen in the blood of certain other conditions, notably nephrosis. In the cases of lipemia retinalis in diabetes studied by Marble and Smith⁶ serial determinations of the total blood fat, total cholesterol, ester cholesterol, and phospholipids in two cases were made In one case the first blood fat value was 14.1 and in the other 7.5 per cent The greatest increase took place in the fatty acids fraction, and the next greatest increase in the cholesterol, and lastly the phospholipids fraction In the nondiabetic patient, a boy aged 16 with acute nephrosis and extreme albuminuria, edema, and plasma cholesterol value of 1410 mg., no visible lipemia was present. The serum protein value was 3.5 per cent Nine months passed before recovery occurred in 1932 On October 19, 1942 the urine showed no albumin, no blood, pus or casts, the plasma protein was 6.02 per cent, and the patient's condition was normal

DIAGNOSIS AND TREATMENT OF DIABETIC COMA

1 **Diagnosis.**—Patients suspected of having diabetic coma belong in the hospital The treatment of diabetic acidosis requires that every facility be used in establishing a diagnosis first of the coma itself and secondly of complicating factors Consultation with a visiting staff member by the intern or resident should be held in every case of severe or complicated coma An error in diagnosis such as the failure to recognize a hypoglycemic reaction or delay in establishing treatment for diabetic acidosis may be fatal Brain tumor, meningitis, sepsis, alkalosis and most important of all hypoglycemia have all been confused with or accompanied diabetic coma Differential diagnosis is imperative

2 **Treatment before Hospital Admission.**—Transfer of the patient to the hospital should be carried out early rather than late The hospital should be one in which laboratory service is available both day and night, holidays and Sundays Insulin should be given prior to admission and indeed in most of the cases reported in Table 4 had

tion of rheumatic disease and it is our contention that this form of therapy is more than symptomatic.⁶ It does not simply modify the symptomatology of rheumatic fever, but distinctly and significantly changes the course of the disease if exhibited in adequate dosage and during the early exudative stage of the disease. Similarly, if given in inadequate dosage and at an inopportune time, it does not produce any favorable effects. More specifically, salicylate therapy is specific

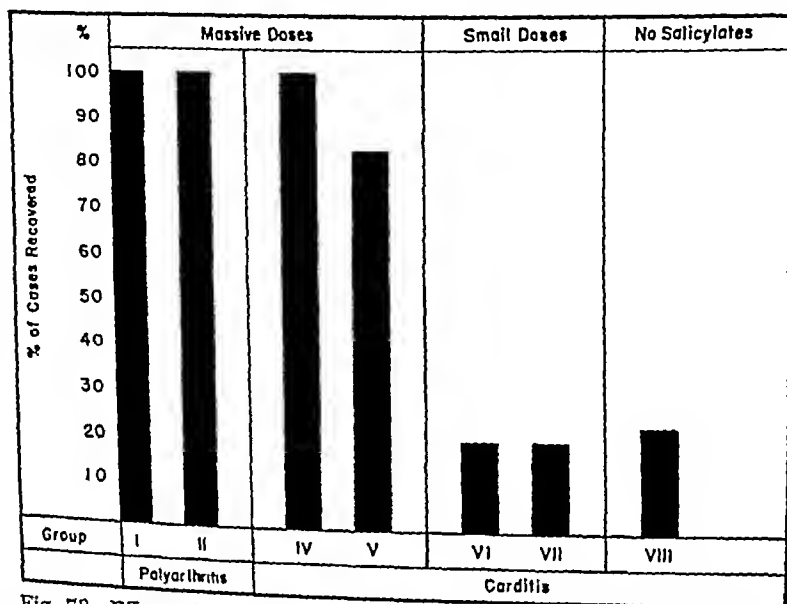


Fig 78—Effect of salicylates on the course of rheumatic activity Group I Children who received intravenous salicylates for rheumatic polyarthritides Group II Children who received massive oral doses of salicylates for rheumatic polyarthritides Group IV Children with carditis who received massive oral doses of salicylates at the onset of the rheumatic episode Group V Children with carditis who received massive oral doses of salicylates, treatment was begun several weeks after onset of carditis Group VI Children with carditis who received the usual small doses of salicylates at the onset of carditis Group VII Children with carditis who received usual small doses of salicylates, treatment begun weeks after onset of carditis Group VIII Children with carditis who did not receive any salicylates during entire period of rheumatic activity (Reproduced from the Journal of Pediatrics, 27 59-68, 1945 Courtesy of the C V Mosby Co)

in its effects when given at the onset of rheumatic fever when the first manifestation is acute polyarthritides, pericarditis or carditis. In such instances, it seems to shorten the activity of the disease and dramatically reduces the disabling effects of the symptoms. Thus a fresh case of rheumatic polyarthritides or carditis can be effectively controlled by adequate salicylate therapy if applied at the onset (Fig 78).

Much has been said about adequate dosage and mode of administration of salicylates. Our observations show that the oral route of ad-

ministration is as effective as the intravenous route. We are impressed by Coburn's observation that favorable results are obtained when the serum level of salicylate is moderately high—300 to 450 micrograms (30–45 mg per 100 cc). This level can be reached by the administration of $1\frac{1}{2}$ grains (0.1 gm) per pound of body weight per day. The dosage, however, varies from patient to patient. One trial determination of the serum salicylate level is usually sufficient to establish the approximate dosage for that patient. The use of sodium bicarbonate in conjunction with salicylates modifies the serum salicylate level curve.¹¹ Larger doses of salicylates or the elimination of the sodium bicarbonate will correct this inadequacy. The points to be noted in this connection are: (1) Enough sodium salicylate has to be administered to reach the desired serum level whatever the mode of administration or method of dosage. (2) The serum level curve must be as far as possible constant. This can be accomplished by giving the drug at two-hour intervals day and night. (3) The serum salicylate level must be kept high until all clinical and laboratory signs of activity have subsided.

Causes of Failure—Our observations further show that adequate salicylate therapy may be ineffective when exhibited during an acute reactivation of a smoldering rheumatic episode. Thus, if a patient develops an acute polyarthritis or carditis during the course of a long protracted rheumatic episode, salicylate therapy will fail to modify the course of rheumatic activity even when given in adequate dosage and for long periods of time. It may indeed give symptomatic relief but will not shorten the duration of the activity of the disease. This may explain the many failures of salicylate therapy reported by various observers. Our observations seem to show that salicylate therapy fails under the following conditions:

1. Inadequate dosage to raise the salicylate serum level
2. Failure to maintain the desired level
3. Large doses of sodium bicarbonate inadequately covered by the administration of larger doses of salicylates
4. The administration of salicylates in cases in whom rheumatic activity has been present for a long period of time
5. Impatience with the continued use of the drug
6. Sensitivity to salicylates and the early occurrence of signs of intoxication
7. Unmindfulness of the fact that, in addition to salicylate therapy, proper nursing and nutritional care is required to attain a favorable result

When the above mentioned factors are taken into consideration adequate salicylate therapy during the course of an onset of the acute exudative phase of rheumatic fever produces specific therapeutic results. This form of therapy gives only symptomatic relief in cases of

rheumatic reactivation and does not seem to affect the course of the protracted, smoldering type of rheumatic activity

Salicylate Intoxication—The hazards of salicylate intoxication have been pointed out repeatedly ^{6, 12, 13, 14 15} Many of the manifestations of intoxication are inconsequential Nausea, vomiting, slight abdominal pain, tinnitus and temporary deafness do not constitute contraindications to the continued use of salicylate therapy On the other hand, symptoms more directly demonstrative of irritability of the central nervous system are ominous and call for an immediate interruption of salicylate administration Hyperventilation, irritability, restlessness, insomnia and confusion are distinct danger signals These symptoms do not seem to be correlated with the above mentioned group of inconsequential symptoms of salicylism The second group does not usually follow the first.

We have not observed severe bleeding resulting from massive salicylate therapy Furthermore, the hyperprothrombinemia which occurs in massive salicylate therapy can be prevented and/or controlled by the use of small doses of vitamin K (1 to 5 mg daily)

In general it may be said that severe salicylate intoxication is a manifestation of sensitivity to the drug on the part of an individual patient Since, however, salicylates are used so extensively in rheumatic fever these "idiosyncrasies" are likely to be observed frequently Increase in ventilation is a sensitive index for intolerance to salicylates This increase in ventilation can be observed clinically without much difficulty When the drug is discontinued during the early stage of hyperventilation, it rarely becomes necessary to administer emergent antisalicylism therapy

Small Doses of Salicylates.—Our observations would seem to show that small doses of salicylates insufficient to raise the serum salicylate level make no palpable impression either upon the symptomatology or the course of rheumatic fever Symptomatic relief from 10 grams of sodium salicylate can, in our opinion, always be shown to be psychological Furthermore, inadequate salicylate therapy does not shorten the course of rheumatic activity even when this therapy is begun at the onset of the rheumatic process Finally, small doses of salicylates do not prevent rheumatic recurrences or reactivations

Salicylate Substitutes.—The startling effects occasionally produced by the use of *aminopyrine* are, in our opinion, accidental It is not a substitute for adequate salicylate therapy and does not produce comparable results in patients who are sensitive to salicylates and are, therefore, deprived of their use The apparent symptomatic relief from aminopyrine occurs most frequently in cases with a moderate febrile course In these instances, the antipyretic effect of aminopyrine may be responsible for the apparent well-being of the patient We have had no experience with other substitutes for salicylates ¹⁶ We are,

however, impressed with the fact that of all the therapeutic measures suggested for rheumatic fever, salicylates thus far have stood the test of time

2 CHOREA

Acute Sydenham chorea is to be regarded as one of the explosive phases of rheumatic fever. As a pure manifestation of rheumatic disease, it is not common. A careful review of the history of a patient with chorea will present evidence to show that the patient has had other manifestations of rheumatic disease either before the onset of chorea or after. In the light of our present knowledge it is not possible to state whether chorea, uncomplicated by other rheumatic manifestations, is associated with rheumatic heart disease since criteria for subclinical rheumatic fever are not clearly defined.

For the present, therefore, the treatment of chorea is entirely symptomatic and no clear-cut evidence can be obtained to show that by relieving the symptoms of chorea, one influences the course of the disease in regard to cardiac damage. Thermotherapy is, in our experience, a specific form of treatment for relieving the acute symptoms of chorea. This thermotherapeutic effect can be reached by either the intravenous injection of typhoid vaccine or by radiant energy, provided that the temperature of the patient is raised to 104° F (40° C) daily for five to seven days. This course of treatment may have to be repeated on two or three occasions. The technic for producing a thermal reaction differs from clinic to clinic and from patient to patient and will, therefore, not be described here. Our observation shows that acute chorea can almost always be controlled by artificial fever therapy, but chronic, mild chorea is not affected by this form of treatment.

Sedation does not measurably influence either the manifestations or the duration of chorea. It might be given only to produce some temporary comfort to the patient. Many other proposed methods of therapy have been tried but, it must be admitted, without any palpable results. Nirvanol has been widely used in the treatment of chorea. Its value, in our experience, is questionable. Its administration is not without danger and its use should be discouraged.

PROTRACTED PHASE OF RHEUMATIC FEVER; SANATORIUM CARE

There is general agreement that the largest number of children having rheumatic disease do not demonstrate the explosive phase either at the onset or during the course of the rheumatic process. Many of these escape diagnosis until cardiac damage becomes manifest. A smaller group, yet numerically significant, are declared as being quiescent, while rheumatic activity is present in the subclinical phase. Still others continue to demonstrate rheumatic activity for months and often years and are unsatisfactorily treated since no specific therapy

is known Furthermore, a mild degree of disability does not give the patient, his family or the physician enough concern to point to a well planned and consistent therapeutic regimen In these instances, it must be admitted, therapy consists of repeated evaluation of laboratory tests in the hope of determining when the activity of the disease has ceased Impatience with bed rest and confinement often modifies clinical judgment and fosters an adherence to nonspecific and, in our opinion, unreliable laboratory criteria of rheumatic activity¹⁷

We should rather focus our attention upon the solid evidence which shows that rheumatic activity, however mild, causes specific and often irreversible cardiac damage In children, the degree of cardiac damage is proportional to the duration of the active process and the failure of its recognition The principle underlying the treatment of the protracted phase of rheumatic disease, therefore, is *the prevention of cardiac damage during the active phase* To this end, various forms of therapy have been advocated—prolonged bed rest, sedation, cardiac supportive medication, carefully controlled sanatorium and convalescent care, and limitation of physical activities of one sort or another for long periods of time It is admitted that despite all such efforts, a large group of patients with protracted carditis demonstrate enormously damaged hearts at the end of the acute episode There is convincing evidence to show that the disappointing results are due to a failure to obtain effective cardiac rest during the course of the smoldering inflammatory process present in the myocardium In addition, it is apparent that cardiac rest must be continued as long as the active process is present Thus, careful and detailed observation of evasive and subclinical manifestations of the protracted phase of the disease are of utmost importance in the matter of preventing progressive cardiac damage For this group of patients, the sanatorium method of care is the therapy of choice¹⁸

Medical Policies Governing the Sanatorium Method of Care.—

These policies are based on the following concepts

- 1 The active phase of rheumatic disease in children is of much longer duration than the clinical signs would seem to show
- 2 The subclinical phase of rheumatic disease deserves as much therapeutic consideration as the well known rheumatic polyarthritis and carditis
- 3 The central aim in the treatment of rheumatic disease is the prevention of cardiac damage, and present medical concepts lead to the belief that this can best be accomplished by an early recognition of rheumatic activity and a careful treatment of the patient during the acute and subacute phases of the disease, however mild the clinical manifestations
- 4 Physical and emotional rest still remain the leading principles in the treatment of protracted rheumatic disease

Since acute rheumatic disease presents bizarre manifestations and unpredictable cardiac emergencies, the therapeutic equipment and facilities of the sanatorium are not unlike those of any well equipped hospital for acute diseases. Medicinal therapy, however, for the present, occupies a place of secondary importance in the sanatorium method of care. Our experience presents a clear clinical demonstration that physical and emotional relaxation is of primary importance in the therapeutic approach to this disease in children. The creation of a proper attitude toward the disease in the mind of the child and his rapid adaptation to sanatorium care, contribute greatly to the progress of repair. The benefits of complete bed rest can be gained only in an atmosphere of contentment and security.

Sanatorium Program—When all signs of activity have subsided, the child is transferred to a convalescent pavilion where a program leading to a rapid resumption of normal activities is instituted. Frequent and careful medical observation for evidence of mild rheumatic activity continues. This period of observation may last weeks or months depending upon the progress in the clinical course of each case. Any deviation from normal childhood growth, development or behavior is viewed with suspicion in regard to the presence of a smoldering, low grade rheumatic infection.

Having passed the rigorous medical observation during the convalescent period, the child is transferred to the "inactive" pavilion. Several years of experience have shown that normal childhood activity is completely harmless to "quiescent" rheumatic hearts. To this observation we found only rare exceptions in the older adolescent group of children in whom cardiac reserve has been permanently impaired. Thus, daily activities during this period of observation are normal. No restriction of physical exercises are made. Careful and repeated medical examinations, however, continue with a view to detecting evasive signs of rheumatic activity. This period of observation continues for a minimum of six months, but in most cases for a period of close to one year.

Duration of Child's Stay—The factors which determine a child's eligibility for discharge from the sanatorium are based on the widely accepted concepts: (1) The younger the child at the onset of rheumatic disease, the more protracted the disease. (2) The more frequent the rheumatic recurrences, the more cardiac damage may be expected. (3) Poor home environment may be a contributing factor to the downward progress of the disease.

The period of residence at the sanatorium will, therefore, be determined by the age of the child, the number and severity of recurrences, and the extent of the detrimental environmental factors in the home to which the child must return. All factors being equal, no child will be considered eligible for discharge until he shows (1)

definite and consistent nutritional improvement and (2) no evidence of rheumatic activity over a period of many months

A critical review of the past seven years of experience with the sanatorium care for the protracted phase of rheumatic disease in children teaches many important lessons. During this period, 626 children suffering from protracted rheumatic activity have completed an average period of residence in the sanatorium. About 537 patient years of rheumatism were studied. Of this period, eighty-eight patient years of rheumatic activity were observed.

Dangers Inherent in Prolonged Institutional Care.—The frequently mentioned dangers inherent in prolonged institutional care for rheumatic children were not encountered during the seven years of observation. *Rheumatic epidemics* were not experienced. The spread of clinical or bacteriologic hemolytic streptococcal upper respiratory infections followed by rheumatic recurrences or reactivations were not experienced in significant numbers. In point of fact, the incidence of both upper respiratory infections and rheumatic recurrences was low. By far, the greatest majority of the sixty-three recrudescences observed were not preceded by any clinical manifestations of upper respiratory infection. The sequential relationship was observed only in several isolated instances.

Psychologic problems usually attributed to prolonged institutional care were only of rare occurrence.

Prolonged rest did not, in our cases, produce complications or sequelae often attributed to long periods of muscular inactivity. In recent years, considerable doubt has been expressed in the literature regarding the advisability of prolonged bed rest in heart disease. It has been suggested that cardiac patients are, as a rule, kept in the prone position too long. In some quarters it is felt that patients having mild rheumatic carditis might do well or better out of bed than at complete bed rest. Our experience with children having protracted rheumatic fever with mild carditis contradicts this contention.

Two groups of children were observed over a period of two years. These groups were comparable as to age, duration of rheumatic history, extent of cardiac damage, and lapse of time since onset of rheumatic fever. Both groups had definite evidence of long-standing mild carditis. One group was kept at complete bed rest during the entire period of activity and the other group was permitted the usual privileges accorded convalescent patients, that is, bathroom privileges, mild recreative games, classroom instruction, dining room privileges, and short outdoor walks. It soon became apparent that the second group was doing poorly. Table 1 presents evidence that this group of children showed an enormous incidence of severe reactivations and seemed to have sustained more palpable cardiac damage than the first group. The contrast between the progress of the two groups was

so great that it became mandatory to abandon the policy of terminating complete bed rest before all clinical and laboratory evidence of activity subsided

TABLE 1°
COMPLETE BED REST IN RHEUMATIC CARDITIS

	Children Who Received Complete Bed Rest during the Entire Period of Rheumatic Carditis (Mild)	Children Who Were Permitted Limited Physical Activities during the Period of Rheumatic Carditis (Mild)
No. of patients	55	50
Average age	10.2	10.8
Average duration of activity (weeks)	22	47
No. of reactivations	2	26
Percentage increase in cardiac enlargements	4	11

* Reproduced from *Am J Med*, April, 1947. Courtesy Yorke Publishing Co., New York.

Results.—The short period of observation and the small number of cases observed preclude the formulation of statistically significant conclusions as to the lasting effects of sanatorium care. However, the close observation of small groups of cases at the sanatorium and of comparable groups of rheumatic children who did not receive sanatorium care, justifies certain noteworthy deductions.

A large proportion of the children treated at the sanatorium were patients from the cardiac clinic and the wards of the Kings County Hospital. The total number of Kings County Hospital children treated at the sanatorium during the seven year period was 373. During the same period of observation, 312 children were chosen from the clinic and wards of the same hospital as controls. Since an unconscious bias may play a significant role in the choice of cases for sanatorium care, painstaking efforts were made in choosing the control group, case for case. No convalescent care of any sort was offered to the control group of children.

TABLE 2
COMPARISON OF TREATED AND CONTROL GROUPS OF CHILDREN AT THE FIRST OBSERVATION

	Control Group	Treated Group
Number of children studied	312	373
At the beginning of period of observation		
Average age (yrs.)	9.35	9.22
Average age at onset (yrs.)	7.38	7.37
Duration of rheumatic history (yrs.)	1.97	2.10
Number of attacks per child	1.67	1.82
Per cent of children with unequivocal cardiac enlargement	12.5	12.5
Per cent of children having active rheumatic disease at the beginning of study	18.7	19.8

The two groups of children were comparable as to age, age of onset of rheumatic history, number of rheumatic attacks, the extent of cardiac enlargement and the incidence and type of rheumatic active infection observed at the beginning of the study period (Table 2). In addition, the two groups compared well as to the type of home environment they had before the study began and at the end of the period of observation.

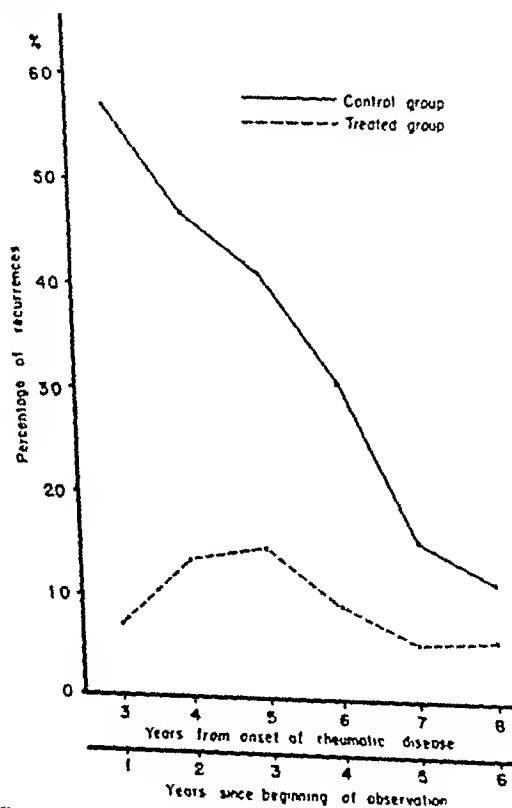


Fig. 79—Percentage incidence of rheumatic recurrences in relation to lapse of time since onset of rheumatic disease (Reproduced from the Am J Med., March, 1917 Courtesy Yorke Publishing Co., New York)

Rheumatic Recurrences—The number of rheumatic recurrences following sanatorium care was significantly smaller than in the control group. Both groups of children show a marked decline in recurrence rate as the lapse of time increases from the onset of the rheumatic disease. The treated group, however, seems to escape a significant number of recurrences. The decrease in recurrence rate in this group is most marked at the beginning of the post-sanatorium period (Fig 79).

Cardiac Enlargement—In our experience the extent of cardiac hypertrophy in children seems to be a more accurate index of cardiac damage than the extent of valvular involvement. Children with large hearts have a much poorer prognosis than those whose hearts are only slightly enlarged. In this study we consider a heart as enlarged only if the enlargement is unequivocal and diagnosed as such both on clinical examination and by roentgen studies.

At the beginning of the period of observation, about 12.5 per cent of both the treated and the control groups of children showed cardiac

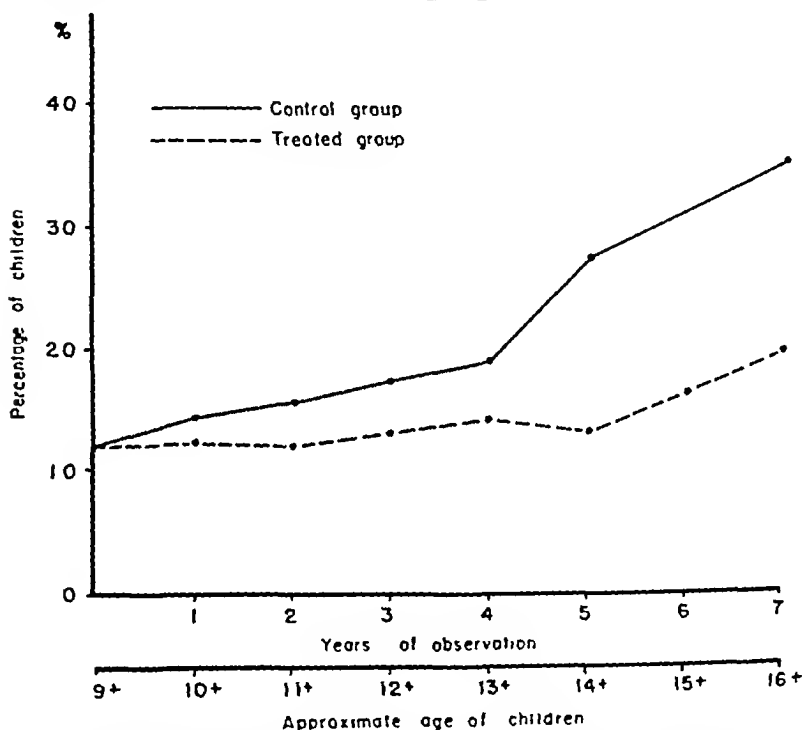


Fig. 80—Percentage incidence of children showing unequivocal cardiac enlargement (Reproduced from the Am J Med, March, 1947. Courtesy J. B. Lippincott Publishing Co., New York.)

enlargement. The average age of our children at the beginning of the study was 9.5 years and the greatest majority of them were seen about two years after the onset of the rheumatic history. As these children were growing older, the percentage incidence of cardiac enlargement rose in both groups, but the increase in the number of patients with large hearts was significantly greater in the control group than the treated group (Fig. 80).

Mortality—It was pointed out by Coombs that before the question

First Hour after Admission	Assign special nurse experienced in coma treatment for the first few hours. <i>Laboratory</i> 1 <i>Urine.</i> Catheterize if necessary Test for sugar, diacetic acid, albumin, coma casts, and pyuria. 2 <i>Blood</i> Test for sugar and CO ₂ content, with emergency report inside the hour White blood count and nonprotein nitrogen also 3 <i>Search for complications</i> A. History to explain cause of coma B. Physical examination (a) State of consciousness, type of respiration, pulse rate, blood pressure, and rectal temperature (b) Look for soft eyeball, dry tongue, dilated stomach, cold and mottled skin, and impacted rectum 4 <i>Insulin</i> 100 units crystalline insulin stat for adults, if blood sugar exceeds 300 mg per 100 cc. and if blood CO ₂ content is 9 millimols per liter or less The dose would be proportionately less in cases of recent onset of diabetes or young children For blood sugars between 600 and 1000 mg, give 200 units additional, and for blood sugars over 1000 mg, give 300 units additional. 5 <i>Gastric lavage</i> Use large tube, aspirate completely and wash stomach with warm water, with greatest care. 6 <i>Intravenous normal saline.</i> 2000 cc. and repeat if indicated by dehydration and blood pressure below 90 mm Hg 7 Keep patient warm Avoid hot water bottle burns.										
Second to Sixth Hour	Occasionally the gravity of the case necessitates repetition of first hour's total insulin in the second hour 8 Repeat blood sugar and CO ₂ determinations after three hours. For rising blood sugar give insulin 50-200 units, according to physician's judgment of prognosis. 9 <i>Fluids by mouth</i> (when possible), not over 100 cc. per hour of ginger ale, orange juice, tea, coffee or broth, to be sipped by patient or spooned by nurse. 10 Soft food such as oatmeal gruel, orange juice or milk diluted half and half with lime water, not to exceed 10 gm. carbohydrate per hour 11 <i>Enema.</i> 12 Record blood pressure, pulse and temperature, note signs of improvement, or the reverse. 13 Urinalysis for sugar and diacetic acid every two hours Record volume										
Sixth to Twenty- fourth Hour	14 Repeat blood sugar and CO ₂ determinations and give insulin 50-200 units if blood sugar and CO ₂ levels are not improving Insulin (crystalline) may now be given according to urine tests every four hours if fall in blood sugar has been satisfactory <table><tr><td>Red</td><td>Orange</td><td>Yellow</td><td>Green</td><td>Blue</td></tr><tr><td>20</td><td>16</td><td>12</td><td>0</td><td>0</td></tr></table> 15 <i>Urinary output.</i> Observe this closely and note with alarm any sign of anuria Treat with 1500 cc. intravenous saline if shock is persisting Repeat as necessary, for anuria associated with hypochloremia, give 50 cc. of 10 per cent salt solution intravenously Never give hypertonic glucose solution to promote diuresis. Beware producing excessive diuresis with consequent loss of base, especially of potassium	Red	Orange	Yellow	Green	Blue	20	16	12	0	0
Red	Orange	Yellow	Green	Blue							
20	16	12	0	0							
Second Day	16 Soft food—diet carbohydrate 100 to 150 gm., protein 50 gm., fat 50 gm 17 Protamine zinc insulin should be begun, supplemented by crystalline insulin in small doses at intervals of four to six hours, as indicated by blood sugar and urine tests										
Third Day	18 Patient should gradually return to the standard diabetic diet for age and weight with carbohydrate 150 to 200 gm., protein 60 to 100 gm and fat 60 to 120 gm										

of life expectancy in rheumatic patients can be answered, at least thirty years must be allowed to elapse between the beginning and the end of observation in a large number of patients. Our numbers are small and the lapse of time even smaller. Nevertheless, the marked difference between the number of deaths in the sanatorium group as compared with the control group of cases is worthy of comment. Of the total of 373 children treated at the sanatorium, eight died of

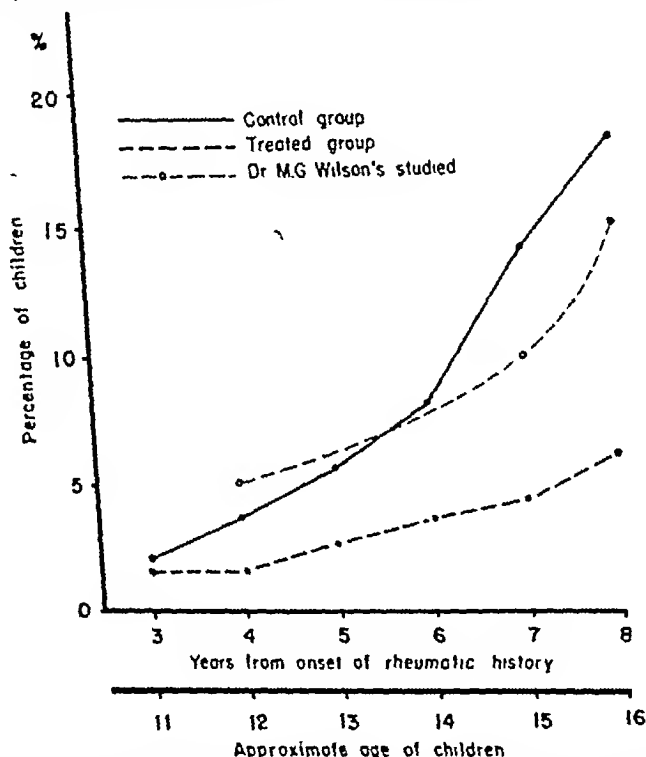


Fig 81—Percentage incidence of deaths in rheumatic children in relation to lapse of time since onset of rheumatic disease (Reproduced from the *Am J Med.*, March, 1947. Courtesy York Publishing Co., New York)

rheumatic disease. Of the control group of 312 children, twenty-one were dead of rheumatic disease at the end of the same period of observation.

The mortality and life expectancy studies of Wilson¹⁰ show that, at the end of the first year from the onset of the disease, 2 per cent of the children died of rheumatic disease, by the fourth year 5 per cent, by the seventh year 10 per cent, and by the end of the eighth year over 16 per cent. Our findings for the control group of children are analogous to those of Wilson. The treated group, however, shows a significantly lower mortality rate (Fig 81).

Summary—It may be stated that seven years' experience with the sanatorium method of care for rheumatic children, suffering from the protracted form of rheumatic fever, seems to show that this type of care influences favorably the course of rheumatic disease in children. It seems plausible to assume that the significant decrease in the recurrence rate at the early stage of rheumatic disease when treated at the sanatorium may in part explain the low incidence of cardiac enlargement and the significantly lower mortality rate observed in the treated group of children.

ACUTE RHEUMATIC FEVER WITH MANIFEST HEART DISEASE

Acute Exudative Carditis.—A large group of children demonstrate obvious clinical evidence of acute carditis uncomplicated by heart failure. While the functional integrity of the heart muscle in this group of cases is impaired, the depletion of the cardiac reserve is not sufficient to manifest signs of failure. It is apparent that rheumatic activity in the heart muscle predominates over the mechanical cardiac disability. Symptoms of heart failure cannot clearly be distinguished from those resulting from the toxicity of the disease. Thus, a moderate amount of dyspnea and the enlargement of the liver may be manifestations of rheumatic activity in the absence of signs of cardiac failure. These cases usually have a low-grade fever, a moderately elevated sedimentation rate and a depressed hemoglobin. The heart is tumultuous and the cardiogram shows a moderate to marked prolongation of the electrical systole.²⁰

Observation of large groups of children with this type of rheumatic fever shows that failure to attain effective cardiac rest during the course of the acute inflammatory process of the myocardium may be responsible for the enormous heart damage observed at the end of the active period. Furthermore, it is obvious that even under the best physical and emotional environment of rest and relaxation, the heart muscle remains overactive during this phase of the disease. Overactivity of the acutely inflamed muscle fiber may be responsible for disturbance of the chemical and mechanical integrity of the heart muscle causing dilatation and impairment of cardiac efficiency. An accelerated cardiac action, a common finding in acute exudative carditis, further depletes cardiac efficacy by diminishing diastolic coronary filling. This accentuates an already existing anoxemia of the heart muscle. Anoxemia of the heart muscle results in further disturbance of cell metabolism. It would seem reasonable to assume that a form of therapy which diminishes cardiac overactivity during the course of the acute exudative process would prevent the damaging results of acute carditis.

Oxygen Therapy—Two years' experience with oxygen therapy in

acute rheumatic carditis suggests that this form of therapy meets the above mentioned requirements.²¹ Oxygen chambers have been provided for this purpose. Children having acute rheumatic carditis reside in a 45 to 50 per cent oxygen atmosphere for ten to fourteen weeks. When a patient is introduced into this atmosphere, cardiac over-activity almost immediately diminished. The marked improvement in the clinical behavior of the patient and the almost immediate removal of all the subjective and objective signs of apparent cardiac insufficiency reflect the profound effect of oxygen therapy upon the cardiac physiology which is so enormously disturbed during the course of acute exudative carditis.

The use of oxygen as a therapeutic agent in heart disease has been studied both in this country and in England. Barach²² and his associates have concluded from their study that in congestive heart failure and in acute coronary thrombosis oxygen is often a life-saving measure. They observed that successes with oxygen therapy occurred more frequently in the degenerative type of heart disease than in the acute inflammatory type of rheumatic carditis. On the other hand, Poulton²³ in England had demonstrated that patients suffering from acute carditis show a marked clinical improvement when treated in a 50 per cent oxygen atmosphere. He found a rapid fall in temperature, pulse rate, alteration of murmurs, diminution in the size of the heart, and significant electrocardiographic changes. The incidence of valvular heart disease was far lower in his treated patients than in the control group of patients.

Our experience with this form of therapy in acute exudative carditis confirms in the main the findings of Poulton. It strongly suggests that oxygen therapy in the exudative phase but with minimal mechanical cardiac disability is an important form of therapy. While the duration of rheumatic activity is not measurably altered by oxygen therapy, cardiac disability is significantly minimized. In addition, the clinical symptomatology of the disease is profoundly changed in favor of a more complete recovery.

Rheumatic Heart Disease with Failure.—It is generally agreed that heart failure in rheumatic disease is always a manifestation of rheumatic activity. Thus, the pattern of failure in these cases must differ from that seen in arteriosclerotic, hypertensive and other forms of heart disease. In rheumatic disease, the degree of failure runs parallel to the severity of the active process in addition to an already depleted cardiac reserve. Experience with oxygen therapy in this group of cases suggests that it is of limited value in the treatment of rheumatic hearts with obvious depletion of cardiac reserve. Furthermore, the usual classical forms of therapy used in congestive heart failure seem to be ineffective in the largest number of cases in this group.

Digitalis Therapy—Clinicians have observed for many years that adequate digitalis therapy in rheumatic heart disease with failure rarely produces the desired result. Some have indeed found that digitalis therapy produces toxic effects before the therapeutic benefits become manifest. Sir Thomas Lewis believed that "the use of digitalis for failure with congestion in rheumatic infection is not recommended." In 1936, Derick stated that "the benefits of digitalis in active rheumatic carditis with decompensation is questionable." In 1930, Schwartz and Levy found that "digitalis does not produce beneficial effects in rheumatic cases with decompensation even during the afebrile period."

A detailed analysis of 100 cases of acute rheumatic carditis with congestive failure leads to the conclusion that adequate digitalis therapy most often fails to effect the desired results. In general, most patients with heart failure observed in this group reacted poorly to digitalis therapy, some showed signs of digitalis intoxication before complete digitalization was reached. A small group of cases, however, showed notable improvement in the cardiac status following adequate digitalis therapy.

We have rarely observed any beneficial effects from digitalis therapy in acute pancarditis with heart failure. The type of digitalis preparation used and the method of administration did not seem to matter and were equally ineffective. Several patients in whom digitalization was attempted with the single dose method developed paroxysmal ventricular tachycardia and in one instance ventricular fibrillation. Our experience with the use of digitalis in this group of cases would seem to warn strongly against it. Similarly, when the presenting symptoms of cardiac insufficiency are those of left-sided failure, the depression of the ST segment and inversion of the T wave on the cardiogram, as well as premature ventricular contractions, occur early in the course of digitalization and complete digitalization can rarely be carried out before intoxication becomes manifest. When the presenting symptoms are significant of both left and right heart failure, adequate digitalis therapy seems to relieve some of the symptoms particularly those which are indicative of right-sided failure. In the rare instances in which the patient shows signs and symptoms of almost true right heart failure, digitalis seems to produce desired beneficial effects.

It is questionable whether rheumatic heart failure ever occurs in the absence of rheumatic activity. Occasionally one is impressed with the fact that all laboratory and clinical evidence of carditis are absent and the patient presents unequivocal signs of advancing failure. While it is admitted by pathologists that histologic examination of the heart of such patients would undoubtedly show evidence of rheumatic activity, it must be assumed that the active process is at a level which

is below the clinical horizon. These cases react in a classical way to digitalis therapy.

In our experience, about one out of every two cases with acute carditis with auricular fibrillation can be controlled with digitalis. The other half of the cases continue to be characterized by a fast ventricular rate with a marked pulse deficit in the presence of adequate digitalis therapy. Further digitalis therapy in this group is accompanied by definite cardiographic and clinical evidence of digitalis intoxication.

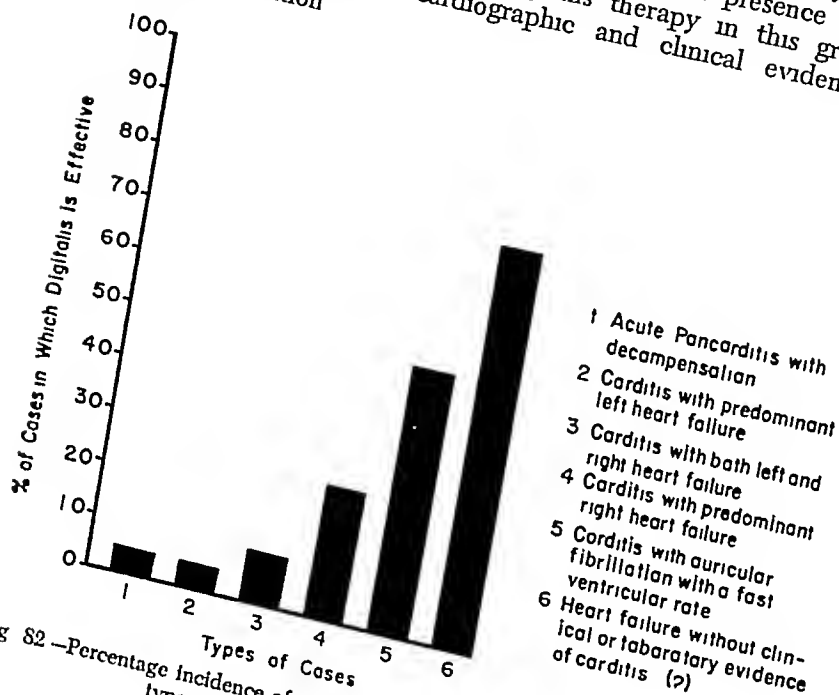


Fig 82—Percentage incidence of successful digitalis therapy in relation to various types of rheumatic heart disease with failure

It is clear from our observations that the use of digitalis in children suffering from rheumatic heart disease with failure is of limited value. In our experience, great care must be exercised in the choice of cases for this form of therapy. In acute pancarditis with failure, and in predominantly left heart failure, digitalis therapy is of no value and its use in these cases is often attended with disastrous results. In patients with predominant right-sided failure digitalis therapy may be tried and is frequently found beneficial. In heart failure without clinical evidence of rheumatic activity, digitalis therapy is always indicated. Patients having acute rheumatic carditis with an uncontrolled auricular fibrillation should always have the benefit of digitalis

therapy In this group, failure to control the fibrillation is significant of the presence of a high degree of rheumatic activity (Fig 82)

Diuretics—An adequate diuresis in acute rheumatic carditis with heart failure is often a life-saving measure Mercurials, in our experience, constitute the most important single form of therapy in this group of patients These diuretics outrank all the others and are definitely superior in the treatment of heart failure with carditis to the digitalis group of drugs

Acute left heart failure with paroxysmal dyspnea in our group of children is almost always relieved dramatically by the judicious and adequate use of mercupurin administered either intravenously or intramuscularly In children, 1 cc. of mercupurin or mercurhydrin is sufficient in most instances to produce the desired diuresis Furthermore, by a careful spacing of repeated mercurial injections, the patient may be kept free of signs and symptoms of failure as long as the active process continues and the patient is potentially decompensated

In acute carditis cases in which the predominating symptoms are those of right heart failure, mercurial diuretics, though not as specifically effective as in the cases of left failure, are nevertheless important in relieving the annoying symptoms In these cases the impression is often gained that the course of the disease may be changed by frequent and adequate relief from the symptoms of right heart failure The removal of dependent edema, ascites, or the decrease in the size of the liver seem to improve cardiac function and increase cardiac reserve

In the so-called quiescent group of cases of heart failure in which digitalis is an effective drug, mercurials enhance the effect of digitalis and in many cases are as indispensable as the digitalis glycosites themselves

There is no rule of the thumb as to how to utilize mercurials in these cases It is obvious that each case must be managed on its own merits Our observation, however, seems to show that mercurial diuretics in acute carditis with failure should be used first to attain "dry weight," that is, to reduce the weight of the patient until adequate dosage of mercupurin no longer decreases the weight of the individual patient But from that point on, a maintenance dose of mercupurin must be continued as long as the activity of the disease persists and the patient is a potential decompensator Such maintenance dose of mercupurin may be continued for months and occasionally for years We have observed no deleterious results from it The dose and the frequency of administration in this group of cases will depend upon two factors (1) The degree of activity of the disease, i e., the higher the degree of activity, the more frequent the administration of mercupurin and also the larger the dose (2) The loss of cardiac reserve If a patient has a low cardiac reserve and minimal rheumatic activity,

he may require as frequent mercurial administration as a patient who has a high degree of rheumatic activity and a higher surplus of cardiac reserve

The use of ammonium chloride in connection with mercurial diuresis is optional, in our experience. Some few cases seem to develop a significantly greater diuresis when ammonium chloride is used in conjunction with mercurial diuretics. We have not been impressed with the use of xanthine diuretics in these cases.

The toxic effects of mercurial diuretics are not often observed in children with acute carditis with failure. Those that occur are of two types: (1) acute syncope—this occasionally follows intravenous use of mercurials, (2) severe symptoms of dehydration, irritability, acidosis and the like—these always occur if the diet and fluid intake are injudiciously limited.

Intravenous Use of Glucose Plus an Increase in the Oxygen Concentration of the Inspired Air—Some few cases of acute carditis with failure do not react favorably to either digitalis or mercurial or any form of traditional therapy for congestive failure. In these, limitation of fluid intake and salt intake, catharsis, excessive perspiration produced by physical or chemical means, mechanical removal of fluids from any of the accumulated depots—none of these methods seem to produce a favorable result. Further analysis of these cases seems to show that the degree of rheumatic activity outstrips the beneficial effects derived from any of the methods of therapy mentioned above. It is clear that accumulation of fluids proceeds at a higher rate than they may be removed by diuresis. Our experience shows that some of the cardiac reserve is dynamically diminished from day to day by the acute diffuse carditis present. These cases do remarkably well when treated in a manner recommended some years back for diphtheritic carditis, namely by the use of concentrated glucose covered by insulin administered in the presence of a high concentration of oxygen. In actual practice, the patient is given 25 cc of a 50 per cent solution of dextrose intravenously, twice daily. This is covered, not fully, by insulin, that is, about 10 units. During the period when this therapy is carried out the patient is kept in an atmosphere of between 45 and 50 per cent oxygen. It is outside the purpose of this paper to discuss the probable mechanism of this form of therapy. We are, however, greatly impressed with its beneficial effects in (1) reducing the toxicity of the disease, (2) increasing cardiac reserve and diuresis, and (3) improving the general clinical behavior of the patient.

Summary—It may therefore be said that the effective treatment of acute carditis with failure predicates careful classification of cases. Digitalis therapy is of limited use except in predominantly right heart failure where the activity of the disease is at a low level, and in

auricular fibrillation with a fast ventricular rate and a marked pulse deficit. Mercurial diuretics outrank digitalis in value in the treatment of rheumatic carditis with failure. The use of a maintenance dose of this form of therapy is of great importance in controlling cardiac decompensation during the active phase of carditis. Many of those cases that have a high degree of carditis and are refractory to all other forms of diuresis react extremely well to the use of concentrated glucose in the presence of a high concentration of oxygen in the inspired air.

SUMMARY

Many forms of therapy for rheumatic fever and rheumatic heart disease have been advocated since the time of Boullard. Few have stood the test of time. This presentation does not constitute a complete analysis of the many forms of therapy which have been preached and practiced in this disease. It is simply a synthesis of many years of experience with large numbers of children suffering from acute rheumatic fever and rheumatic heart disease observed frequently and carefully under a therapeutic regimen which seems to have produced results that compare favorably with any of the methods of treatment thus far proposed. This experience teaches the lesson that the outlook for the acute rheumatic child is indeed good, provided that the type of treatment instituted bears a rational relationship to the particular phase of disease manifest at the time of treatment.

Furthermore, it is obvious that whatever the "specific" forms of therapy proposed in this communication may be, the outcome will depend in good measure upon the "nonspecific" nursing, nutritional and emotional care that the patient receives at the same time.

From the therapeutic standpoint, therefore, the following observations are made:

1. The latent period of rheumatic disease remains, for the present, without effective therapy.

2. The acute exudative phase can be almost "specifically" controlled with adequate salicylate therapy. Thermotherapy in acute chorea is a specific form of treatment for relieving the symptoms but it cannot be said, from our present evidence, that it influences the course of rheumatic disease in these patients.

3. The smoldering phase of rheumatic fever is most effectively managed with careful sanatorium type of care. Evidence seems to point that this type of care prevents progressive cardiac damage and eliminates many reactivations.

4. It is proposed that oxygen therapy favorably modifies the outcome of acute rheumatic carditis in its exudative stage when signs of heart failure are not manifest.

5. Digitalis therapy for acute rheumatic heart disease with failure is of limited value. Judicious use of mercurial diuresis outranks digi-

talis in the treatment of these cases. A maintenance dose of mercurial diuretics is of importance in carrying the patient through the active phase of the disease when he is potentially decompensated.

6. Acute toxic carditis in which acute exudative phase dominates over the evidence of failure and the rheumatic process is universally distributed, frequently fails to react to any form of therapy except intravenous administration of glucose with insulin in the presence of a high concentration of oxygen in the inspired air.

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been given by phone order with the result that blood sugar levels were actually somewhat lower than they would otherwise have been. The patient should be kept warm in transit.

3 **Insulin.**—In Table 3 is summarized an outline of the treatment of diabetic coma. The most important decision in the first hour of treatment has to do with the size of the insulin dose. The patient, having been admitted and placed in a bed warmed and provided with hot water bottles outside the blankets and with equipment assembled for the giving of salt solution subcutaneously and intravenously and the presence of diabetic coma having been established, insulin should be given immediately. Two facts make this decision difficult. (a) Resistance to insulin increases as acidosis advances, and (b) the law of diminishing returns applies to the efficiency of insulin so that the results from second and later doses may sometimes be obtained only

TABLE 4

BLOOD SUGAR LEVEL CORRELATED WITH INSULIN DOSE IN 188 COMA CASES
October 21, 1940, to October 1, 1946

Blood Sugar on Admission, Mg per 100 Cc.	Cases	Average Insulin in First 24 Hrs., Units
1300-1600	2	1219
1000-1300	5	815
600-1000	42	380
400- 600	65	251
200- 400	74	162

by increasing the size of the first one. Patients with diabetes of long duration and long in coma and a blood sugar level of more than 500 mg will require large insulin doses whereas younger patients with recent diabetes may require as little as 30 to 50 units.

A striking relation exists between the level of the blood sugar and the total amount of insulin required in the first twenty-four hours of treatment as indicated by Table 4. Here it is seen that among 188 coma cases treated during the six years from October, 1940 to October 1, 1946, 1219 units were required for two cases in which initial blood sugar values were between 1300 and 1600 mg. The average insulin required declined steadily from this high level in accordance with the lower blood sugar level. Many a patient receives enough insulin but owing to delays or indecision in the first few hours too little insulin is given at the time when it will count the most. Insulin given six to eight hours after admission in an unconscious patient is worth much less per unit than what it was worth during the first hour after admission. The significance of the insulin dose in the first three

MENINGOCOCCEMIA WITHOUT MENINGITIS IN CHILDREN

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MENINGOCOCCEMIA without meningitis has received little attention in pediatric journals and textbooks. The condition is, however, not infrequent. Now that effective therapeutic agents are available, early diagnosis is imperative. It is our purpose, here, to present seventeen cases seen on the Children's Medical Service, Bellevue Hospital, between January 1, 1942 and July 1, 1946. All had positive blood cultures for meningococci. In none was there reason to believe that meningitis existed and in fifteen the spinal fluid was in every way normal.

HISTORY

Though isolated cases had been previously reported,^{1, 2} credit is due to Herrick³ for calling attention to the frequency of this syndrome and for giving a clear description of the clinical picture. In 1919 he reported 315 cases of meningococcemia at an Army camp. In approximately 40 per cent of the patients the diagnosis was made before meningitis developed. The duration of the premeningitic stage varied from a few hours to several weeks. Approximately 5 per cent of the patients never developed meningitis.

Following Herrick's publication a large number of isolated case reports and several reviews^{4, 5, 6} have appeared. In 1945, Goldring and his associates,⁷ surveyed the experience at the St. Louis Children's Hospital and the St. Louis Isolation Hospital. In the seventy-nine cases observed at the St. Louis Children's Hospital, meningitis did not develop in ten. Three of the ten patients died with fulminating symptoms. The remaining seven responded promptly to treatment.

Age.—Excepting for epidemics such as occur in military barracks, meningococcal infection is predominantly a disease of early childhood. Fifty-four of the seventy-nine patients reported by Goldring were less than 5 years of age. In our series of nonmeningitic meningococcemia the youngest patient was 6 days old. Ten of the seventeen patients were less than 3 years old.

Family Incidence.—Multiple cases of meningococcal infection in

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the same family are considered uncommon. However, there are a number of reports of instances in which two or more members of the same family were affected.^{8,9} In two of our cases a sibling was affected. The possibility of meningococcic infection in other members of the family should be seriously considered.

CLINICAL PICTURE

The more important clinical and laboratory data in our cases are shown in Table I.

The clinical features of meningococcemia are (1) history of a common cold lasting from a day to several weeks, (2) abrupt onset, (3) high fever; (4) chills, convulsions, twitching at the onset, (5) nausea and vomiting, (6) appearance of a hemorrhagic rash within a few hours after the onset, and (7) pains in the joints or abdomen.

The *temperature* is generally high, between 104° and 105° F, at times even higher. It is apt to remain high until treatment is instituted.

Joint pains are not common in children with nonmeningitic meningococcemia. Only two of our patients complained of arthralgia. The pain is evanescent and affects principally the larger joints, the knees, ankles, wrists and elbows. There may be simply pain on motion or there may be redness, swelling and signs of fluid in the joint. The aspirated fluid is generally sterile but it may be purulent and contain meningococci.

The most striking clinical manifestation is the *rash*. It was present in every patient in this series. An exceptional case was that of a child admitted to the hospital some years ago because of fever and drowsiness. The temperature remained between 102° and 103° F for four days and gradually fell to normal. A rash was never observed. A blood culture, taken on admission and reported after the child had been discharged, revealed meningococci. The only medication given was aspirin.

It is easily possible to miss cases of meningococcemia when no rash is present. Though it has been the custom on the Children's Medical Service at Bellevue Hospital for many years to take blood cultures in all patients with fever of obscure origin, it is not our general practice to incubate these cultures in a carbon dioxide rich atmosphere except where meningococcemia is suspected. Failure to take this precaution may readily lead to falsely negative results.

In adults a number of cases have been reported in whom no mention of a rash was made.⁴

Occasionally the rash is maculopapular (two cases in our series) but it is generally hemorrhagic. There may be petechiae (seven cases), often combined with larger skin hemorrhages (seven cases). In one patient there were only large skin hemorrhages.

TABLE 1—CLINICAL AND LABORATORY DATA IN SEVENTEEN PATIENTS WITH MENINGOCOCCÆMIA

Case Number	Age Years	Initial Symptoms	Character of Rash	Maximum Temperature, Degrees Fahrenheit	Initial Leukocyte Count		Maximum Agglutination Titer		Remarks
					Total	Polymorpho-nuclears, Per Cent	Day of Disease	Titer	
1	6 days	Fever, rash	Petechial	103.2	20,000	75	Not done		Blood count done after sulfadiazine therapy had been given for 4 days. Smear of o. petechia showed gram-negative intracellular cocci.
2	2	Fever, convulsion	Maculopetechial	105	26,000	95	Not done		Smear of petechia showed gram-negative intracellular cocci.
3	3	Fever, vomiting, twitching	Generalized petechial	105.4	15,900	87	Not done		Smear of petechia showed gram-negative intracellular cocci.
4	2	Fever, abdominal pain	Generalized petechial	106.0	28,000	81	Not done		Smear of petechia showed gram-negative intracellular cocci.
5	2½	Fever, chill, vomiting	Maculopapular	104.8	21,600	84	Not done		Smear of petechia showed gram-negative intracellular cocci.
6	2½	Fever, vomiting, chill	Generalized petechial	101.5	18,000	82	Not done		Smear of petechia showed many white blood cells.
7	6	Fever, headache, pain in ankle	Generalized petechial	104	22,200	96	Not done	1,256	
8	2½	Fever, drowsiness, pain in knee	Generalized maculopapular	104.4	17,000	72	6	neg	Smear of petechia showed gram-negative intracellular cocci.
9	10	Fever, drowsiness	Generalized petechial	104	21,000	88	11	1,600	
10	1½	Chill, fever, vomiting	Petechial on arms and back	105.8	1,800	11	1	1,600	Agglutination titer negative on second day.
11	7	Fever, vomiting, drowsiness	Generalized petechial	105	16,000	97	6	neg	Died. Brother had meningitis.
12	1½	Fever, vomiting, convulsion	Generalized maculopetechial	104.4	20,800	86	11	1,800	
13	5	Fever, vomiting, abdominal pain, joint pain	Generalized maculopapular	103.2	22,000	85	7	1,800	Agglutination titer negative on fourth day.
14	2	Fever, chill, convulsion	Generalized maculopetechial	104.4	20,800	86	Not done	1,800	Agglutination titer negative on second day.
15	7½	Fever, headache, delirium, vomiting, general hypercæsthesia	Generalized maculopetechial	104.8	22,600	72	5	1,400	
16	5	Cyanosis, rash	Generalized purpuric	—	—	—	Not done	—	Dead on arrival in hospital.
17	1½	Fever, vomiting	Generalized petechial	106.4	1,600	94	Not done	—	Died.

The rash is usually profuse. It may occur over any part of the skin and often involves the mucous membranes of the eyes and mouth. It appears abruptly and spreads over the body irregularly. The spots may appear in cycles.

The *spleen* is not enlarged in children with meningococcemia.

Though the clinical picture is a fairly constant one, there are exceptions. Mild cases are occasionally seen. During the past two years we have observed seven children whose clinical picture resembled that seen in meningococcemia but in whom positive blood cultures were unobtainable. They all had fever and a petechial eruption. Recovery following treatment with sulfadiazine was prompt. It is probable that the meningococcus is the etiologic agent in a considerable number of children whose disease is diagnosed as purpura simplex or, when joint manifestations are present, as purpura rheumatica.

Fulminating Cases (Waterhouse-Friderichsen Syndrome).—The onset is abrupt with collapse and the rapid extension of a hemorrhagic eruption. The patients are apprehensive and restless and the sensorium remains clear until the end. There may be edema of the face. The extremities are cold. The temperature is generally low grade—between 100° and 102° F—but it may be high or it may be normal. Gastrointestinal symptoms such as vomiting and diarrhea are frequent. Oliguria or anuria is of especially grave significance.¹⁰ A striking symptom is cyanosis without apparent cardiac or pulmonary involvement. The outcome is usually fatal.

Three of the seventeen patients in this series, aged 15 months, 18 months and 5 years, respectively, presented this clinical picture. They all died.

Chronic Meningococcemia.—A number of cases of chronic meningococcemia have been described which last for months and even years. Dock¹¹ described a patient who had a septicemia which lasted seven months. The patient finally developed meningitis and died. One of Heinle's patients¹² had a history strongly suggestive of recurrent meningococcemia over a period of fourteen years. The disease is characterized by intermittent fever, usually low grade, an eruption which is generally hemorrhagic and arthralgias or septic arthritides. There may be lesions of the endocardium, myocardium, pericardium, lungs, sinuses, eyes and epididymis. Meningitis may eventually develop.

Meningococcemia occasionally develops after recovery from meningococcus meningitis. Fox¹³ reported a patient who developed meningococcemia seventy-nine days after clinical recovery from meningitis. A third episode occurred forty-three days later.

LABORATORY AIDS IN DIAGNOSIS

Leukocyte Count.—The white blood cell count is the most valuable quick laboratory aid in the diagnosis of meningococcemia. As a rule

extremities The left ankle was swollen The spleen was slightly enlarged The temperature was 101° F

The hemorrhagic lesions, some of which were bullous, spread, and some sloughed, leaving ulcers

The platelets were reduced, the highest count being 55,000 per cu. mm. The prothrombin, bleeding and coagulation times were prolonged. The white blood cell count was 18,600 with 69 per cent polymorphonuclear cells Blood culture showed a gram-negative rod which grew only on media enriched with blood, but failed to type with the usual influenza sera.

Shortly after the patient's admission the temperature rose to 103° F and remained at this level. New hemorrhages appeared in the skin, with necrosis and ulceration The boy received several transfusions On the seventh hospital day sulfadiazine therapy was begun The temperature fell gradually, reaching normal in three days. It rose from time to time during the next two weeks but thereafter remained normal. The platelet count rose to a normal level on the twelfth hospital day Extensive skin grafting was necessary for the lesions on the legs

When the skin hemorrhages are extensive, thrombocytopenic purpura and leukemia must be considered. Demonstration of gram-negative cocci or numerous polymorphonuclear cells in a smear from one of the skin lesions will establish a diagnosis quickly

Difficulties arise in the cases in which the rash is macular or maculopapular Here rickettsial infections and measles must be ruled out Of considerable diagnostic aid is the white blood cell count which is generally elevated with a high proportion of polymorphonuclear leukocytes in meningococcemia

COMPLICATIONS

Complications are uncommon Occasionally hemorrhagic necrosis of the skin takes place One patient in this series (Case 1) developed a purulent discharge from the eyes which contained gram negative cocci

TREATMENT

When meningococcemia is suspected, a blood culture should be taken and treatment started immediately It is necessary to take the blood culture first since it is generally impossible to culture meningococci once sulfonamides have been given

The drug of choice is *sulfadiazine* The dosage in a child is 1 gm per 10 pounds of body weight each twenty-four hours One fourth the daily dose is given every six hours The initial dose is a double one, that is, half the daily dose The drug may be given pulverized and suspended in food or in sugar water If the child refuses to take the drug or is comatose, it may be suspended in water and given by stomach tube, or sodium sulfadiazine may be given in solution by nasal tube Intravenous therapy (5 per cent sodium sulfadiazine) acts more quickly but the time required to give an intravenous injection is generally greater than the time saved Sodium sulfadiazine may be given in 5 per cent solution subcutaneously

meningococcemia They were not made regularly in our patients They may be taken with a curved, protected swab to avoid contamination with oral bacteria, or else by passing a small straight swab, protected by a nasal speculum, through the nasal passage to the nasopharynx Rabbit's blood agar is an effective medium

Of the various types of meningococci, Type I is found much more often than the other types in patients with meningococcic disease. In the seven patients in this series in whom typing was done all were Type I

Agglutinin Test.—The demonstration of agglutinins in the serum of patients with meningococcal infection is of diagnostic value when blood cultures are negative According to Dowling and co-workers,¹⁶ the test is specific for the type of meningococci The titer rises in the second and third week and generally falls to 0 between the twenty-fifth and thirtieth days, but the times are variable

Similar results were obtained by Thomas, Smith and Dingle,¹⁷ who stress the diagnostic value of demonstrating a rise in titer during the course of the disease, since positive reactions may be found in carriers and in contacts

According to Falk and Applebaum,¹⁸ an agglutination titer of 1 to 100 or greater is significant They obtained positive reactions in 75 per cent of the patients tested The reaction is type-specific. False positives are sometimes obtained in gonococcus infections

Agglutination tests were done in nine of the seventeen patients in this series in the Laboratory of the Department of Health, New York City, by Falk¹⁸ Significantly elevated titers for Type I meningococci were obtained in seven cases (Table 1) In two cases, both done on the sixth day of disease, the agglutination titers were negative Tests were done in six of the seven cases in which blood cultures were negative Five of the six patients yielded significantly high titers In the sixth case a negative titer was obtained on the fourth day of disease.

DIFFERENTIAL DIAGNOSIS

In the presence of an acute onset with high fever and a hemorrhagic eruption the most likely diagnosis is meningococcemia Other forms of sepsis may occasionally give a similar clinical picture This is true especially of infection with hemophilus influenzae Such a case is the following

Septicemia Due to an Influenza-like Organism Skin Hemorrhages with Sloughing Thrombocytopenia. Recovery after Sulfadiazine Therapy—M. A., a 5 year old boy, complained of pain in the right heel two days before admission At the same time there was fever up to 102° F On the next day a hemorrhagic eruption appeared on the shins and feet and at the same time there was nosebleed. On admission, the child looked acutely ill. There were dark purple raised petechiae over both legs anteriorly and over the feet, and a few on the upper

extremities The left ankle was swollen The spleen was slightly enlarged The temperature was 101° F

The hemorrhagic lesions, some of which were bullous, spread, and some sloughed, leaving ulcers

The platelets were reduced, the highest count being 55,000 per cu. mm The prothrombin, bleeding and coagulation times were prolonged The white blood cell count was 18,600 with 69 per cent polymorphonuclear cells Blood culture showed a gram-negative rod which grew only on media enriched with blood, but failed to type with the usual influenza sera.

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The large doses of sulfadiazine should be continued for forty-eight hours, or for twenty-four hours after the temperature has reached a normal level. The daily dosage may then be halved and continued at this level for at least four days.

Sulfadiazine is given with an equal amount of sodium bicarbonate. The child should have fluids freely, parenterally if necessary.

Penicillin has no advantage over sulfadiazine and it has several disadvantages, e g, the discomfort associated with administration of the drug and the greater expense. According to Meads and associates,¹⁹ penicillin is as effective as sulfadiazine in meningococcemia without meningitis but it is not nearly so effective in meningococcus meningitis.

Antimeningococcus serum is not necessary.

If hyperpyrexia is present, small doses of *aspirin* and *sponging with alcohol* are effective. *Phenobarbital* is useful if there are convulsions or twitchings.

Waterhouse-Friderichsen Syndrome.—Treatment against shock and bacteremia is combined with adrenal cortical hormone administration.¹⁰ To combat shock, *heat*, *stimulants* and the *antishock position* are used. The child should receive from 300 to 500 cc. of *parenteral fluid* during the first twenty-four hours, about one half of it as plasma.

Sulfadiazine should be used in large amounts. The initial dose should be 3 to 4 gm given as quickly as possible. The daily dose should be 1 gm per 5 pounds.

As substitution therapy, 5 cc of *adrenal cortex hormone* should be given every two hours.

Prophylaxis.—Though multiple infections with the meningococcus in the same family are not common, they occur often enough to make prophylactic administration of *sulfadiazine* to other members of the family advisable. One of the three children in this series, who died with fulminating meningococcemia, was infected by a brother.

The efficacy of prophylaxis has been amply demonstrated.²⁰

For prophylaxis 0.5 gm of *sulfadiazine* should be given twice a day for two days.

SUMMARY

Meningococcemia without meningitis is a not infrequent syndrome in children.

The onset is abrupt with hyperpyrexia, chills or convulsions, drowsiness, nausea or vomiting, at times pains in the abdomen or joints and the appearance of an eruption which is usually hemorrhagic.

Laboratory aids are the elevated white blood cell count with the polymorphonuclear cells usually above 80 per cent, smear of a hemorrhagic lesion which often shows organisms or many white blood cells, the positive blood culture, and the agglutination titer.

The treatment of choice is with sulfadiazine, promptly administered in adequate amounts

The prophylactic administration of sulfadiazine to other children in the family is recommended

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hours was brought home to us when we compared the mortality rate for diabetic coma cases treated prior to 1940 and since that time. Thus in 478 cases treated between 1923 and August, 1940, the average amount of insulin given in the first three hours was 83 units. Deaths numbered fifty-eight, or 12 per cent. In 185 cases treated from 1940 to 1946 there were four deaths or 2.1 per cent. The average insulin given during the first three hours in this latter group was 215 units during that time. During the succeeding hours the plan outlined in Table 4 is usually followed but it must be stressed that each patient must be studied individually and no ironclad rule should be applied without regard for the complications or the degree of dehydration, and for the rapidity of change in that patient.

TABLE 5

SCHEDULE FOR ADMINISTRATION OF INSULIN

Benedict reaction				
Insulin (units required)				
Red	24	Orange	20	Yellow
			16	8
				Green
				0
				Blue

In Table 5 is shown a schedule for the administration of insulin at intervals of two to four hours according to urine tests. The fundamental principle in the use of insulin is to give enough insulin to obtain the pharmacological effect, namely utilization of the excess glucose present in the body fluid, deposition of glycogen, oxidation of glucose and thereby cessation of excessive ketone formation. The most reliable evidence that this change in metabolism is taking place is a decline in the blood sugar level.

The supply of carbohydrate in the form of glucose in the blood and extracellular fluid of the diabetic patient during coma is not generally appreciated. In a patient described by Root and Leech¹ the following analysis is shown in Table 6.

TABLE 6

THE AVAILABLE SUPPLY OF CARBOHYDRATE IN THE BLOOD AND EXTRACELLULAR FLUID DURING COMA

(Woman 73 kg. liver 1800 gm, muscles 25 kg., 21 liters blood and extracellular fluid, blood sugar 960 mg., total blood acetone bodies 76 mg. per 100 cc.)

Normal		Diabetic	
Gm		Gm	
108 (6.0%)	18 (1.0%)	18 (1.0%)	18 (1.0%)
150 (0.6%)	75 (0.3%)	75 (0.3%)	75 (0.3%)
17 (0.08%)	210 (0.96%)	210 (0.96%)	210 (0.96%)
4	24	24	24
279	327	327	327

Liver glycogen
Muscle glycogen
Blood and extracellular fluid (glucose)
Skin (glucose)
Total grams of carbohydrate

It is seen that in this patient 327 gm of carbohydrate were estimated as present in the blood and extracellular fluid. If to this amount

ACTIVE IMMUNIZATION IN PEDIATRICS

PHILIP COHEN, M D *

THIS clinic will be concerned with the consideration of active immunization in children. By active immunization I mean the generation of antibodies by an organism in response to the introduction of an antigen, no matter by what route. Active immunity results in antibodies which tend to persist for months or years. A cardinal and invaluable feature of active immunity is that years after the original immunization a single injection of the antigen will quickly reactivate the production of the antibodies. This stimulating, or booster, injection will raise the titer of protective antibodies, in a matter of days, from a low, inadequate level to a protective titer which is often higher than the original immune titer. In contradistinction, passive immunity, which consists of the injection of preformed antibodies, is of short duration and not susceptible to reactivation by a stimulating dose of antigen. In my opinion, we have not properly availed ourselves of the fact that booster injections can stimulate further production of antibodies long after the onset of active immunization.

The past decade has witnessed important changes in the technic of active immunization. Preparations of antigens have been continually perfected, and the dosage and timing of the administration have changed for the better. These innovations were accelerated by the impact of war, which served as a vast laboratory for testing the efficacy of new methods. The lessons learned have been incorporated into civilian prophylaxis, with promise of further improvements. The pediatricist, who necessarily performs large scale routine immunization, should be in the van in the study of the efficacy and the innocuousness of the most recent prophylactic measures.

DIPHTHERIA

Diphtheria remains a most important epidemiologic problem. It has been demonstrated by myself and collaborators¹ as well as by others,² that the past generation has undergone a subtle change for the worse in adult immunity to diphtheria. The mass of data collected by Schuck³ (1914 to 1923) showed that about 85 per cent of adults were immune to diphtheria in this preimmunization period. The institution of routine diphtheria prophylaxis on a massive and widespread scale has resulted in a striking decline in the morbidity and mortality

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of diphtheria. As a concomitant phenomenon, however, the carrier rate has declined to a proportionately low figure. The reduction of the carrier state in an artificially immunized community, with necessarily lessened exposure to toxigenic diphtheria bacilli, has resulted in a loss of the artificially acquired immunity in a high percentage of adults. It has already been noted that there is a trend to diphtheria increase in many sections, where outbreaks of diphtheria have been reported chiefly in adults, here and abroad, in civilian and in military life.⁴ The New York City newspapers of October 17, 1946, publicized reports from the health commissioners of the state and city that diphtheria morbidity and mortality have noticeably increased throughout the nation, and stress the need of further immunization.

Epidemiologists have commented that the diphtheria problem of the future is concerned with the immunity of the adult.⁵ Epidemics of adult diphtheria should not occasion surprise, for studies have demonstrated that artificial diphtheria immunity confers sufficient but declining protection for a period of three years. After this period there is a perilous fall in the level of immune titer unless there is a stimulation of immunity by artificial or natural means, the latter normally through the medium of the vanishing carrier. My investigations at Beth Israel Hospital, in a large group of young women, indicate that as of today, about 50 per cent of adults are Schick positive.

Important corollaries follow these observations. It was formerly confidently assumed that, since the adult is nearly always immune to diphtheria, the newborn baby is similarly immune, since he is endowed with his mother's antibodies at birth. Immunization of the infant had hence been postponed for six to nine months, after which period he presumably lost his passively acquired immunity. Indeed it was believed that in the presence of passive antibodies, active immunization would prove ineffective. Since proof has been adduced that in many areas 50 per cent or more of adults are susceptible, the immunity ascribed to the newborn baby often rests upon a false assumption. Recent tests by me on a group of 100 babies substantiated this contention, for 50 per cent of infants below 6 months of age were Schick positive.

These facts and findings should logically lead to a change in diphtheria prophylaxis. To guarantee the transfer of immunity from mother to baby, it is necessary to ascertain maternal immunity. If the mother is Schick positive, diphtheria toxoid should be administered during the seventh and eighth months of pregnancy at intervals of two to three weeks in doses of 0.1, 0.2, 0.5, and 1 cc. This conversion to a Schick negative state is transmitted to the baby to persist six to nine months. If the mother is Schick negative, a single stimulating dose of 0.2 cc. of diphtheria toxoid elevates her antitoxin titer to a highly effective level, to the benefit of her baby. The pediatricist has little

opportunity to pursue this practice. It properly lies in the province of the obstetrician and general practitioner.

Schick tests routinely performed on mothers before and after delivery and in newborn infants reveal that the mother is a better reactor and indicator than her baby. If the Schick test is positive in the mother or baby we begin to immunize the baby at 3 months of age. Since the period of prophylaxis and the attainment of an immune titer require three months the baby remains susceptible for its first six months of life. The only known way to remedy this undesirable situation is to immunize the mother during pregnancy.

Our method of diphtheria prophylaxis in infants is administration of three injections of diphtheria toxoid in doses of 0.5 cc, 1 cc and 1 cc at intervals of three to four weeks. Unlike alum toxoid, the plain toxoid rarely causes a reaction. The Schick test is performed six months later. For years we have not seen a positive Schick test following this prophylaxis. Every three years a single inoculation of diphtheria toxoid is given, and continued as long as a state of immunity is desired, into adult life and the period of pregnancy, if so desired.

TETANUS

Tetanus, a dread disease also caused by a toxin, was characterized by a singularly low incidence in the last war. Routine tetanus toxoid prophylaxis was so effective in producing adequate immunity that not only was tetanus virtually absent in this war but there was seldom need of administering tetanus antitoxin. The army employed the fluid formalized toxoid in three doses of 1 cc each at intervals of four weeks. The navy favored alum toxoid, given in two doses, 0.5 cc at four week intervals. A routine stimulating dose was given annually, with the additional precaution of an extra stimulating dose with every change of locale and before combat engagement. A point worth noting is that fluid toxoid should be given if there is need for a quick rise of the antitoxin content, for alum toxoid acts slowly, and is therefore less useful as a rapidly stimulating dose.

In pediatric practice tetanus immunization procedure is the same as that employed by the army and navy. It is recommended routinely for children who spend their summers in camp, to avoid needless injections of tetanus antitoxin which are too often given for inevitable injuries, with the attendant risk of producing dangerous allergies. Children of the hyperkinetic type who frequently suffer trauma, and youngsters living in the country intimately in contact with soil, may also benefit by the administration of tetanus toxoid. The fluid toxoid is almost devoid of reactions except in the cases of a few children who develop allergy to the preparation as a result of repeated inoculation. The alum preparation causes more frequent reactions and nodule formation but spares the child an injection.

WHOOPIING COUGH

Whooping cough is the most important contagious disease of childhood for which we employ bacterial vaccine prophylaxis. The vaccine developed by the Sauer technic administered in adequate doses has materially reduced the incidence of pertussis in children above 1 year of age. Ample data has been accumulated to prove this point beyond reasonable dispute. It probably has also modified the course of the disease in many children in whom prophylaxis has not been entirely successful.

As in diphtheria, the problem of protection of the infant has not yet been satisfactorily solved. Data has been accumulated proving that the majority of adults (80 per cent) are not immune to pertussis.¹ It follows that 80 per cent of babies are susceptible to whooping cough from birth, for they must lack immunity if their mothers do. It has been the custom to institute pertussis prophylaxis at 6 months of age. When vaccine therapy has been completed and immunity obtained, the infant is nearing 1 year of age. Here again is a dangerous gap in immunity against a disease which takes its highest toll in infancy. The only known method of conferring immunity upon the infant is immunization of the mother during the last trimester of pregnancy. The active maternal immunity is passively transferred to the baby. Since it is a passive immunity it lasts but a few months, after which period (at 4 to 5 months of age) active immunization of the infant should be initiated.

There is much evidence pointing to the fact that a young organism, such as the infant, is a poor antibody producer, even if inoculated with potent antigens. Some years ago Sauer reported unsuccessful attempts to actively immunize infants below 6 months of age against pertussis.⁴ The incidence of the disease was the same in the immunized as in the unimmunized group. Laboratory tests also demonstrated defective antibody formation in these young infants. A more recent attempt to immunize infants at 1 to 3 months of age against pertussis yielded more encouraging data.⁷ Three injections of 0.2, 0.3, and 0.5 cc of an alum preparation totaling 40 billion bacilli per cc resulted in positive agglutination tests in about 80 per cent of the infants two to four months after the completion of prophylaxis. The morbidity and mortality of the vaccinated group (3,793 cases) was significantly lower than in a control group. It may be that the slowly operating alum preparation used was more effective in these young infants than the generally employed Sauer vaccine. Further observation by the New Orleans group and by other investigators employing a similar immunization procedure confirmed the growing opinion that very young infants may be capable antibody producers.⁸ Nevertheless, Sauer, adopting a similar technic for this age group, reported that only 31 per cent of young infants so inoculated had a positive complement fixation

test Further data is needed to determine whether it is feasible to begin pertussis prophylaxis in babies so soon after birth

The usual procedure in pertussis immunization is to inject a Phase I vaccine at three to four week intervals until 90 to 120 billion organisms have been administered, the amount varying with the age and the size of the baby This requires 6 to 8 cc of a 15 billion per cc. preparation, 4.5 to 6 cc of a 20 billion per cc preparation The entire procedure requires three to four inoculations, the number depending upon the presence or absence of reactions It appears that alum preparations are equally effective in smaller doses Studies upon similar groups of children are now in progress in my clinic upon the comparative immune titer obtained by alum preparations given in a dosage two-thirds that of fluid vaccine Were it not for greater reaction and nodule formation, the alum preparation would undoubtedly be preferable These reactions can be obviated to some extent by deep subcutaneous injections using a vaccine warmed and well shaken, followed by massage of the inoculated area

My present inclination regarding pertussis prophylaxis, as with diphtheria, is to begin immunization at an earlier age than heretofore At three to four months of age immunization may be instituted in infants in good condition If the infant is Schick positive a preparation of diphtheria toxoid combined with the pertussis vaccine is employed This combination of antigens has previously not been included in the armamentarium of prophylaxis for very young infants

TYPHOID FEVER

Typhoid fever prophylaxis by vaccine inoculation has been admittedly effective for many years The past war afforded another brilliant example of the efficacy of this vaccine, for again there was a very low morbidity in those vaccinated⁹ It should be interpolated that all immunity is relative, be it natural or artificial immunity. An antibody titer effective under normal and ordinary circumstances may be insufficient and overwhelmed in the presence of a virulent infection or intensive exposure Thus typhoid fever has been reported in individuals properly inoculated and with protective immune titers, but infections are much fewer than in unvaccinated individuals under the same conditions, and the course of the disease tends to be milder⁹ Many instances have been recorded (and observed by me) of two or more attacks of diseases like measles, scarlet fever, whooping cough, mumps, and other diseases which are known for their capacity to produce a lasting high level of immunity This relativity of immunity applies to all immunity against disease

Innovations and improvements in typhoid prophylaxis have recently been introduced Rawling's typhoid strain has been supplanted by the superior Panama 58 antigen,⁹ which has been put to commercial

use The dosage remains the same, 0.5 cc, 1 cc and 1 cc, but intervals longer than one week have proven superior In pediatric, unlike military practice, there is seldom urgency of time, and an interval of two weeks is preferred The dosage given to a child may be computed on the basis of weight ratio to the adult, or slightly more than this calculation calls for Laboratory studies have shown that the former method of three inoculations every three years yields a titer of protective antibodies which sink to a low level long before the expiration of the three year interval Only 20 to 25 per cent of individuals retain an adequate titer of protective antibodies two or more years after typhoid inoculation¹⁰ A single injection of 0.5 cc of typhoid vaccine given annually succeeds in elevating the protective antibodies to the optimum level in 100 per cent of cases¹⁰ I consider the best practice to be administration of annual booster injections of 0.5 cc of typhoid vaccine after the initial trio of inoculations This practice should be adopted for children going to camp, for a constantly high level of immunity is thus obtained instead of the former uncertain fluctuating titer The reactions incurred by this annual method are fewer and less severe than with the old three shot system

SMALLPOX

Smallpox vaccination is accomplished by the use of a preparation containing a live but attenuated virus It is one of the few instances in which a live organism is used to induce active immunity in children It has been established that there is no natural, probably not even passive immunity to smallpox Donnelly successfully vaccinated newborn infants thereby confirming that there is no immunity of the newborn to smallpox¹¹ A comparative study of the potency of culture and calf-grown virus was made in this group of vaccinated newborns Revaccination two or three years later resulted in successful takes in 73 per cent of those vaccinated with the calf virus Vaccination with a virus culture took in only two out of thirty-six cases This study not only attested to the susceptibility of the newborn to smallpox and the superiority of the calf-grown virus for vaccination, but also demonstrated that the immunity may wane as early as two to three years after successful vaccination

When smallpox is prevalent it is important to bear these facts in mind Every infant should be vaccinated and failures should not be construed as indicating immunity It is advisable, if possible, to wait an appreciable period, about a month after the unsuccessful vaccination, before revaccinating. If the interval is shorter, the site of the unsuccessful vaccination may light up and take as the second successful vaccination evolves Thus two vaccinia will develop concomitantly with proportionately greater systemic effects, local reaction, and scar formation In the presence of an epidemic or on the eve of travel to

a state or country where smallpox occurs, previously vaccinated individuals should be revaccinated even if the interval is less than five years. I have several times observed successful revaccination without the expected modification in children vaccinated two or three years previously. My belief is that vaccination should be repeated at the slightest indication, for if immunity persists, there is little or no reaction, if, however, immunity is lost or largely lost, the resulting take and immunity will be a source of satisfaction. The duration of immunity after vaccination is extremely variable, ranging from two years to many years, perhaps for the duration of life.

Normally the initial vaccination is performed at 3 to 8 months of age at a time when the infant is in excellent health, the season favorable and the skin in normal condition. I try to avoid vaccination during uncomfortably hot weather and during seasons of rampant or endemic infections. The puncture method of vaccination yields a smaller area of reaction with a smaller scar and less systemic reaction. I have rarely used the intracutaneous method for lack of scar formation deprives one of definite proof of lack of immunity. I prefer the arm for the area of vaccination in both males and females. It is safer, less disfiguring and less prominent than leg vaccinations. No dressing is used after the first day. A shield or a covering of any sort is strictly forbidden. I have been fortunate, aided by the insistence of the above precautions, never to have had any infection or ill effects from a smallpox vaccination.

INFLUENZA

Influenza is another virus disease, for which an inactivated virus preparation has been invoked in the last few years. Because of newspaper predictions of epidemics, pediatricists are receiving numerous inquiries as to the efficacy and desirability of the new vaccine. From available data it may safely be assumed that nearly every adult has been infected at some time with pandemic influenza.¹² Hence, only one inoculation of 1 cc of virus vaccine need be given since it acts as a reactivator or a booster injection of waning immunity. Within one or two weeks after inoculation over 90 per cent of subjects show a sharp increase in circulating antibodies,¹² an effect comparable to that of booster injections for diphtheria, tetanus and other diseases in which an active immunity may be produced. One year later the antibody titer is still above the prevaccination level.¹³ Nevertheless, the definite decrease of antibodies at the end of a year and the prompt, sharp response to a single injection would indicate the need for annual booster injections. Surveys have shown that the rate of incidence in vaccinated groups is considerably lower than in control groups (25 per cent).¹⁴

The technic for the preparation of the vaccine is quite different from the method ordinarily employed for vaccine preparations. The

live virus is incubated on the extra-embryonic fluid of the developing hen's egg. As a result of processes of adsorption, diffusion and centrifugation, the final preparation of the virus contains little or no egg protein. Tests are being made by precipitation methods to determine whether egg protein has been completely eliminated to avoid allergic reactions in sensitive individuals. It may be the better part of wisdom, at present, to test egg allergic individuals with the preparation, and if the reaction is positive, to proceed with caution.

There is little available data on influenza virus vaccination in children.¹² It may even be incorrect to assume that the very young child has been previously infected with the virus. If this assumption be false, two inoculations at intervals of two weeks may offer better protection to the young child. The dose for children may best be gauged by weight ratio, as in other vaccine therapy. I have been inoculating children up to 3 years of age with 0.25 cc., up to 10 years with 0.5 cc., and the older group with 1 cc. of the vaccine. In my limited experience the reactions in children have been below expectation. Slight headache, transient chilliness and fever, and soreness of the arm for about a day have been observed by me. Collective data is now needed to determine the efficacy of this vaccine in children in the presence of a proven epidemic.

It must be emphasized that the influenza virus vaccine protects only against influenza A and B. Parents are informed that other respiratory infections, virus or bacterial, will be unaffected by this prophylaxis. To protect against recurrent respiratory infections, often loosely called "colds," a bacterial vaccine, "catarrhal vaccine" has been employed for years parenterally and laterally orally. The genuine cold, a virus infection, must be uninfluenced by such measures. It is claimed, but not proved, that secondary respiratory infections may be influenced for the better by the use of a vaccine containing most of the common respiratory flora. Such a vaccine is not infrequently used for this purpose in pediatric practice, but its efficacy can only be conjectured through empirical observation. There is no scientific data demonstrating increased immune titers against respiratory disease after such inoculations.

RICKETTSIAL DISEASES

Potent vaccines against rickettsial diseases have been recently developed, notably against typhus fever and other spotted fevers.¹³ These vaccines are prepared on a yolk sac medium, and hence precaution must be taken when such vaccines are injected into egg allergic individuals. These vaccines are administered to children in amounts proportionate to the adult dose of 1 cc. Two injections are given at intervals of two weeks. Typhus fever is not common in this country, but traveling to areas of infection is sufficient indication for such vaccination in children. The spotted fevers (Rocky Mountain fever) are

indigenous to certain sections of this country I have employed this vaccine for several children visiting infected sections. My cases are too few in number to warrant immunological conclusions, but there have been no untoward reactions.

YELLOW FEVER, PLAGUE AND CHOLERA

The armed services used effective vaccines against yellow fever (a virus vaccine) and also vaccinated at times against plague and cholera.¹⁵ Such vaccines are rarely given to children in this country as there is no need for them. I have never found occasion for such vaccination. Nevertheless, a trip to a section where these diseases are prevalent would be sufficient indication for the administration of such prophylaxis. Since the human serum component has been eliminated from the yellow fever vaccine, there has been a cessation of reports of jaundice following such vaccination.

SCARLET FEVER

Scarlet fever active immunization has not proved popular in eastern United States. The frequency and severity of reactions after scarlet fever prophylaxis have been a distinct drawback. The injection of an unmodified toxin, generally five to seven times, in amounts varying from a few hundred to hundreds of thousands of skin test doses have caused in 10 to 15 per cent of cases such reactions as nausea, fever, vomiting and rash, comparable to a case of mild scarlet fever.¹⁶ Infrequently, the alarming symptom of joint pains has been reported. On the other hand, such immunization has decidedly reduced the incidence of scarlet fever. This prophylaxis should be given for the protection of nurses and workers in contagious hospitals, and for those intensively exposed to scarlet fever. Because of reactions, the numerous injections, the often temporary nature of the immunity, in conjunction with the fact that scarlet fever has for years been of a mild character in the East, I am not given to the use of scarlet fever prophylaxis. Should matters change and scarlet fever assume a more malignant form, I would advise prophylaxis in spite of its disadvantages. Perhaps newer preparations, (alum and tannic acid precipitation), now under investigation, will offer a happy solution.¹⁸ If the precipitates prove effective, only three injections, provoking few reactions, will be necessary. Laboratory tests have demonstrated an immunity duration of four years after inoculations of these products. Other toxoids, previously tested in three doses at three week intervals, have not been as effective as the toxin preparation usually employed.

COMBINED PROCEDURE; OTHER ROUTES

It should not be assumed that these immunization procedures must be given individually and in succession, necessitating much expendi-

ture of time and inconvenience to the patient. Pediatricians have been leaders in proving the efficacy of combining immunization procedures. Even before the war investigations showed that each antigen combined in a mixture produced an immune titer equal to or greater than that effected by the antigen injected individually. Pediatric practice and the vast military immunization have yielded ample and convincing confirmation of the effectiveness of simultaneously injected vaccines.

The infant and child, like the soldier, should have his prophylaxis completed in a brief period, for it is wiser to abbreviate as much as possible the period of absent immunity. The accepted and best practice today is to immunize the infant simultaneously against diphtheria, pertussis and, if desired, tetanus. I have also mixed toxoid with other vaccines, such as typhoid, with no ill effects. I have not yet ventured to mix vaccines or toxoid with rickettsial or live virus vaccine. Nevertheless, it may be entirely feasible to employ such mixtures, with the possible exception of the vaccine virus.

Introduction of antigen by a route other than subcutaneous, intracutaneous or intramuscular has not been generally invoked in pediatric practice. It may well be that other forms of administration, notably by nebulization or aerosol technique, for direct immunization of localized regions, such as the respiratory tract, may yield better immunity against localized diseases. Experimental work along these lines has yielded promising results. Future studies may more emphatically prove this point and lead to a wider use of such methods in immunization practice.

SUMMARY

In summary, it may be restated that modern active immunization favors the simultaneous administration of different antigens either in a mixture of two to three antigens, or by separate injections at different sites. The previous weekly interval between inoculations has been generally lengthened to two to four weeks. The active immunity, waning often to an inadequate and nonprotective level, should be stimulated by a booster injection every year, or every two or three years. This interval is determined by the need for immediate protection, and the desire for a constantly high immunity instead of an uncertain and fluctuating one. The trend is also developing of maintaining a continually high level of immunity by giving annual injections instead of three injections every three years, as in typhoid fever prophylaxis. Vaccination against smallpox should be performed in the presence of outbreaks of this disease, unless the last successful vaccination was performed less than three years before exposure. By these methods safety is attained with a minimal expenditure of time and the omission of many painful injections to the child.

I believe that active immunization of the infant will be given at

is added the extra glucose present within the cells, the figure should probably be increased by another 50 to 100 gm. The important feature in treating such a patient is to bring about a return of glucose oxidation. Mere conversion of the excess glucose in blood and body fluid into glycogen or fat will have no beneficial effect. During the emergency the one objective is to bring about actual glucose oxidation. The patient received 500 units of insulin, the blood sugar fell from 960 mg to a normal value within the next twelve hours, the ketone production came to an end because glucose oxidation took its place. During the first six hours her caloric needs (75 calories per hour) amounted to 450, derived chiefly from protein and fat. The patient cannot be expected to oxidize more than 8 or 10 gm per hour since even a normal man will oxidize no more no matter how much glucose is given by vein so long as he is at rest. The administration of glucose during the first six hours of treatment of diabetic coma cannot possibly bring about any greater oxidation of glucose than the excess glucose already present in his body fluid makes possible. When a large excess of glucose is present either in the form of hyperglycemia or when injected as glucose solution and a large amount of insulin is given, some of the glucose will be transformed into glycogen, but recent evidence indicates that a much larger proportion of that glucose is converted into fat. This point has been well discussed by Wood-yatt.⁸ Reduction of glucose to fatty acids probably occurs largely in the liver and so might be an indirect step in oxidation. However, this fatty acid is frequently converted in liberal amounts to fat. Indeed working on this problem in rats Mackay and Drury⁹ have shown that the major part of the carbohydrate intake is stored as fat and not glycogen. Stetten and Bozán¹⁰ studied the turnover of glycogen in the liver and carcass of rats and only 3 per cent of the dietary glucose was handled by way of glycogen and at least 10 times as much was used to synthesize fatty acids as was used to form glycogen. Later working with rats made diabetic by alloxan the same workers concluded that an impairment of fatty acid formation from glucose in such diabetic rats explained a large part of the urinary glucose. One may expect insulin to increase fat formation from glucose. Root and Carpenter had previously shown that glucose administered by vein in diabetic acidosis fails to raise the respiratory quotient and no evidence of increased oxidation of glucose occurs unless insulin is given. The final evidence against the use of glucose during the stage before an adequate amount of insulin has been given has been recently reported by Lukens¹² when he produced degeneration of the islands of

an earlier age (3 to 4 months) than in the past (6 to 9 months) This still leaves the infant unprotected against some diseases (notably pertussis and often diphtheria) for the first six months of his life Prenatal immunization by active immunization of the mother during pregnancy, can solve this important problem

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GAMMA GLOBULIN IN PEDIATRICS

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BLOOD is composed of cells and plasma which can be readily separated by such simple physical means as centrifugation. About 65 per cent of the plasma is protein. It is this element which is chiefly responsible for the benefits obtained in plasma transfusions. The protein in plasma is not a single protein but a mixture of proteins, chiefly albumin, fibrinogen and alpha, beta and gamma globulins. These proteins differ in molecular size and structure and in physiologic and therapeutic properties. The separation, concentration and drying of the different components of plasma by the use of physicochemical methods was accomplished by Edwin J. Cohn¹ and his associates at Harvard University. A number of these components have been tested clinically, among them gamma globulin.

PROPERTIES OF GAMMA GLOBULIN

Gamma globulin makes up about 11 per cent of the total proteins of plasma. Its therapeutic value is due to the fact that all antibodies against infectious disease which are present in plasma appear to be concentrated in the gamma globulin. There are laboratory procedures for the determination of the concentration of certain antibodies in a solution. Enders² has made determinations of the concentration in gamma globulin of antibodies against typhoid, pertussis, influenza A, poliomyelitis, diphtheria and scarlet fever. Tests for the presence of antibodies against other diseases have been made by other investigators. There is no known laboratory test for the determination of the concentration of measles antibodies. The therapeutic value of an antibody must, of course, be determined by clinical trial.

CLINICAL USE OF GAMMA GLOBULIN

Measles.—PROPHYLAXIS—The chief use of gamma globulin today is in the prophylaxis of measles. One would expect a high concentration of measles antibody in gamma globulin since about 90 per cent of the urban population has had measles by age 30 and since the immunity conferred by measles is a solid one. Clinical trials have confirmed this expectation. A study³ to determine the comparative value of gamma globulin in the prophylaxis of measles was begun in New York City

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early in 1944. Since there had been no previous published reports of dosage, a decision was made on theoretical grounds to use 2 cc as a uniform dose and modify the amount if necessary. This was injected into more than 800 susceptible household contacts to cases of measles between the ages of 6 months and 6 years. Seventy-nine per cent of them developed no measles and 21 per cent developed modified measles. None developed severe measles. The younger the child the greater was the protection. With increase in age the percentage of no measles cases declined and the percentage of modified measles cases rose. Thus at 1 year of age, 90 per cent of contacts injected with 2 cc of gamma globulin developed no measles and 10 per cent had modified measles, whereas at 5 years of age, with the same dose, 60 per cent did not get measles and 40 per cent had modified measles.

Since the greatest danger from measles is in the very young, it is a wise plan to try to protect them completely. On the other hand, it must be remembered that gamma globulin confers a passive immunity which lasts for a period of about three weeks only. There is no known agent, at present, which will confer active immunity. However, a child who has had measles becomes permanently immune. There is evidence to believe that modified measles also causes the development of active, permanent immunity. It is therefore advisable to administer enough gamma globulin to give modified measles to the older children, in whom the danger from measles is not great, so that they can develop an active and lasting immunity to the disease. A dose of 2 cc seems to fulfill both needs.

The injection is given intramuscularly either in the arm or in the buttocks using an 18 or 20 gauge needle. The usual precaution should be taken of drawing back on the plunger after the needle is in situ, to make sure that a vein has not been entered. Reactions are rare. The globulin may be given at any time between the fourth and the eighth day after initial exposure. The day on which the rash first appears in the source case is usually the fourth day of the disease. The dosage of gamma globulin for the prophylaxis of measles may also be adjusted on the basis of body weight.^{4, 9} The recommended doses are 0.08 to 0.1 cc per pound of body weight for protection and 0.02 to 0.025 cc per pound for modification.

When measles breaks out in the ward of a children's hospital, the ward may be kept open to further admissions if all susceptible contacts are injected with gamma globulin in a dose no less than 0.1 cc per pound of body weight. Should secondary cases occur, then all susceptible children on the ward at that time who have not previously been injected, as well as those who were injected more than two or three weeks before, should receive gamma globulin in the same dosage.

Two other substances have been widely used in the prophylaxis of measles. One is *convalescent measles serum*. It confers a high degree of

protection. Its disadvantages lie in the fact that it is difficult to obtain and that the doses administered are large. The other substance is *placental globulin*. Its disadvantages are also two. One is that the degree of protection is less than with either gamma globulin or convalescent measles serum. In the comparative study previously referred to³ it was found that 23 per cent of those injected developed severe measles. The second disadvantage is the severity of reactions. In the same study, reactions occurred in 41 per cent of those injected. These were both general, consisting of fever and restlessness, and local, consisting of pain, swelling and redness at the site of inoculation. By contrast, reactions in the children injected with gamma globulin occurred in only a fraction of 1 per cent.

Placental globulin is sold on the market as "immune globulin, human." It should not be confused with gamma globulin which is referred to as "human, immune serum globulin." Gamma globulin is distributed commercially by one biological firm in a 2 cc vial.

TREATMENT—The use of gamma globulin in the treatment of measles has been reported by Stokes, Maris and Gellis.⁴ They used doses ranging from 5 to 35 cc in a group of sixty-one individuals ranging in age from 10 months to 34 years. Thirty were injected after the rash had started, and modification appeared in thirteen. The rest were injected when Koplik spots were present, but before the rash had appeared. Modification of the disease appeared in twenty-four and no rash in two cases. The authors point out that final conclusions about the value of gamma globulin in treating cases of measles cannot be reached until larger groups have been treated.

Acute Infectious Hepatitis—Acute infectious hepatitis (catarrhal jaundice) is a disease which has occurred in large outbreaks in military personnel as well as in the civilian population. Although infectious hepatitis has a low mortality, it causes considerable disability. There is also some evidence that it may cause serious late results. Where large groups of children are congregated as in institutions, camps or schools and an outbreak of infectious hepatitis occurs, it would be desirable to limit the spread of the disease. Stokes and Neefe⁵ injected a group of fifty-three susceptible boys and girls and some adults in a camp where an epidemic was in progress. They obtained a good deal of protection when the globulin was injected early in the incubation period, in a dose of 0.15 cc per pound of body weight. About eight times as many cases occurred in the control as in the injected group. Havens and Paul⁶ had a similar experience in a children's home. They used slightly smaller doses (between 0.06 and 0.12 cc per pound of body weight) in a group of ninety-seven susceptible children between the ages of 6 and 16 years. Twelve times as many children developed jaundice in the control as in the inoculated group. The results of these investigations indicate an important

use for gamma globulin in limiting epidemics of infectious hepatitis. Gamma globulin has not been found effective in the *treatment* of cases of infectious hepatitis even when administered early in the disease and in large doses.

Scarlet Fever.—Gamma globulin is at present being tried in the treatment of scarlet fever in a number of contagious disease hospitals. Previous reports have appeared in the literature on the use of convalescent scarlet fever serum in the early treatment of scarlet fever. These have generally been favorable. With the use of such serum there have been a rapid drop in temperature, subsidence of the toxic state and diminution in the percentage of complications. Since the concentration of scarlet fever antitoxin and antistreptolysin in gamma globulin is from two to five times as great as in scarlet fever convalescent serum, one is led to believe theoretically that the globulin should be of value. Since no reports have as yet been published, the evaluation of its use must wait the gathering of data and their statistical analysis. However, preliminary reports indicate that gamma globulin is probably of value both in the prevention and in the treatment of scarlet fever.

Whooping Cough.—Whooping cough convalescent serum has been used for a number of years in the treatment of pertussis. In the past few years there have appeared reports on the use of hyperimmune human whooping cough serum both in the passive prophylaxis of infants and children exposed to pertussis and in the treatment of those suffering from it. Adults are hyperimmunized to pertussis by receiving a course of injections of whooping cough vaccine over a number of months. They are then tested for antibodies to pertussis. If the titers are high, they are bled and their sera pooled. The hyperimmune serum is used in 10 to 20 cc doses. The one disadvantage of the use of such serum, outside the cost, is that the injection of large quantities, particularly if repeated, causes pain and discomfort. Recently the hyperimmune serum has been subjected to fractionation. The gamma globulin obtained from the hyperimmune serum contains the antibodies in concentrated form. Such gamma globulin is now available commercially in a vial of 2.5 cc, which is equivalent to 25 cc of the hyperimmune serum.

Poliomyelitis.—Bahlke and Perkins⁷ of the New York State Health Department studied the effect of injections of gamma globulin in the preparalytic stage of poliomyelitis. They gave large doses, from 20 cc for children under 1 year of age to 100 cc for those over 12. Their work was well controlled. No benefit whatever to the injected group was detectable. The same percentage of paralytic cases developed in the injected as in the control group.

German Measles.—German measles is one of the minor communicable diseases of childhood. There are practically no deaths from it.

and complications are rare. In recent years, however, reports have appeared in the literature of the birth of children with congenital cataract, congenital heart disease and other congenital anomalies, to mothers who contracted German measles early in their pregnancy. Although the evidence is not completely convincing, the association is frequent enough to make it desirable to prevent the development of German measles in pregnant women. No published reports have appeared on the use of gamma globulin in the prophylaxis of German measles. Our experience is limited to a study (with S. Frant and D. D. Rutstein) of a group of forty infants between the ages of 1 and $2\frac{1}{2}$ years in a foundling home, who had been exposed to German measles. Alternate children were injected with 5 cc of gamma globulin one to four days after exposure. Six children developed German measles eleven to nineteen days later, all controls. The group studied was too small, and the exposures in an institution are too irregular to warrant a definite statement as to the significance of the results obtained. They appeared sufficiently suggestive to make us feel that a more extensive study would be justified.

In another unpublished study,¹⁰ twenty-nine of fifty-eight exposed children in an institution were injected with 2 cc of gamma globulin. In from twelve to twenty-three days after administration of the gamma globulin five cases occurred among the injected children and seven cases in the controls.

Chickenpox.—Chickenpox is also a communicable disease with practically no mortality and with few complications. However, because of its high degree of contagiousness and the long incubation period, it frequently ties up a children's ward for a long time. A prophylactic agent would be of great value to children's hospitals. In our German measles study we were able to observe the effect of the administration of 5 cc of gamma globulin to twelve out of twenty-nine infants all of whom had been exposed to chickenpox as well as to German measles. The attack rate in the injected group was not significantly different from that in the control group.

Mumps.—The concentration of the mumps complement-fixing antibody in gamma globulin is fifteen to thirty times that of the plasma from which it is obtained.² However, it is only from one-thirteenth to one-quarter that of mumps convalescent serum.³ Theoretically one should not expect any beneficial results from the use of gamma globulin in the prevention of mumps. In an actual test it was found to be of no value.⁴ It also did not prevent the development of orchitis even when administered in large doses. However, gamma globulin concentrated from a large pool of mumps convalescent serum, when administered in doses of 20 cc did influence the occurrence of orchitis. About three and one-half times as many cases of orchitis occurred in the uninoculated as in the inoculated patients.¹¹ The dose used was

equivalent to 400 cc of mumps convalescent serum or 4500 cc of normal plasma. Obviously the use of such large quantities of blood for a single dose is not practical even if effective

Other Uses.—The uses to which gamma globulin can be put have by no means been exhausted. Experiments are needed to test its value for a number of diseases as this has been determined for measles and infectious hepatitis. Its preparation from convalescent sera is still in its infancy. No serious difficulties have been met by serum centers such as those in Chicago and New York in maintaining a constant supply of measles and scarlet fever convalescent serum. It should be possible to obtain convalescent sera of different communicable diseases from contagious disease hospitals in the United States for fractionation. The preparation of gamma globulin from the plasma of individuals hyperimmunized to certain diseases, as is now done in pertussis, could be extended. Here, however, cost will be an important item since voluntary donors will probably be difficult to obtain. Finally, the further purification of gamma globulin so that it can be administered intravenously may enhance its value in therapy.

SUMMARY

Gamma globulin is the prophylactic agent of choice in the prevention and attenuation of measles. It is also of value in the prophylaxis of epidemic hepatitis. There is reason to believe that it may be of help in the prophylaxis and treatment of scarlet fever. Its value in the treatment of measles has not been sufficiently demonstrated, and there is insufficient evidence to judge its value in the prophylaxis of German measles. In the early treatment of poliomyelitis to prevent paralysis it has been without effect. It has also been of no value in the treatment of epidemic hepatitis. It does not appear to protect children exposed to chickenpox or to mumps. In huge doses it may prevent the complications of mumps.

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ATELECTASIS IN POLIOMYELITIS

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This paper is a preliminary report of four cases of atelectasis occurring in poliomyelitis patients with respiratory embarrassment. It is the plan of the authors to report further cases, and to review the literature at a future date

Atelectasis is one of the most frequent, and certainly the most serious complication of cases with respiratory difficulties. The respiratory embarrassment may be caused by paralysis of the intercostal muscles, the diaphragm, or both. The degree of atelectasis differs with every case, but when it occurs, it becomes a serious threat to the life of the patient. Most of the cases of atelectasis are due to two factors, (1) inability of the patient to cough adequately and (2) the presence of an infection in the respiratory tract. Since the patient cannot cough because of partial or complete paralysis of the diaphragm, he becomes unable to keep the respiratory tract free from secretions which are produced in increasing amounts when an infection exists.

One theory of the etiology of atelectasis is that mucus present in the respiratory tract may obstruct the bronchus either partially or completely. When the mucus partially obstructs the bronchus, a ball valve action is produced which lets air out but not into the alveoli. This action, thus, empties the obstructed lung area of air, producing the atelectasis. When the mucus plug completely obstructs the lumen of the bronchiole, it acts as a cork, allowing the passage of air in neither direction and the air which is present in the alveoli is absorbed. In either case the collapsed lung area then becomes fertile soil for the growth of pathogenic organisms, and a pneumonia may rapidly develop. Because of the great danger of a fatal ending, the treatment of all cases of atelectasis in poliomyelitis should be considered a medical emergency.

Inasmuch as the signs, symptoms, course, and treatment of atelectasis in poliomyelitis may vary considerably, we are presenting in detail four cases which illustrate some of these variabilities.

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Langerhans in cats by giving continuously large injections of glucose.* If a normal cat can be so injured, what can be expected of the diabetic patient in coma whose islands of Langerhans are already under great strain. For many reasons, therefore, no glucose is advised until after the first six or eight hours when sufficient insulin has been given to bring about a decline in the blood sugar to a nearly normal level. In the next day or two if the patient continues to be too ill to take natural foods by mouth, then feeding by means of glucose solution must be employed while sufficient insulin is being given to provide for its normal utilization.

4. Fluid and Salt.—Dehydration, hemoconcentration, low blood pressure, dryness of the skin and softness of the eyeballs are the distinguishing features of the shock syndrome in severe diabetic coma. It depends in considerable part on the loss of sodium and water consequent upon insulin deficiency. Therefore, as in the outline, we recommend immediate administration to unconscious patients of 1500 cc. of normal salt solution intravenously and 1500 cc. subcutaneously. This may need to be repeated more than once. In patients with impending anuria a safe rule is to leave the needle in the vein of the arm or the ankle and let salt solution flow continuously one liter per hour until anuria is relieved. It should be noted that this intensive treatment is designed and intended for use only in those patients with extreme dehydration indicated by anuria, low blood pressure, soft eyeballs and shock. For such patients sometimes 50 cc. of 10 per cent salt solution may be given intravenously and repeated.

5. Gastric Lavage.—Rarely should a patient in true coma be treated without drainage of the stomach and lavage with warm water inside the first hour or two after admission. The fact that a patient has not vomited is not a contrary indication. Usually the stomach is dilated and distended with fluid containing food remnants and dark changed blood, gray or black in color. All too often the death of a coma case has been attributed to pulmonary edema when in reality sales at the bases of the lungs are really due to gastric contents which have been aspirated or have flowed into the lungs. A large Ewald tube is preferred to the small duodenal tube.

6. Enemas.—A cleansing enema should be given immediately and in severe cases repeated.

7. Food.—The administration of food such as orange juice and oatmeal, both of which contain potassium, should begin within six or

* See also the first article of this symposium for comprehensive discussion by Ricketts.

CASE I

A 16 year old, white male, was admitted on November 1, 1945

Past History Noncontributory

Family History Mother and father living and well

Present Illness Patient became ill on September 22, 1945, with general malaise, acute coryza and headache. He had a low grade fever until September 27, when he began to vomit. On September 29 he developed a stiff neck and weakness of both legs, and a diagnosis of poliomyelitis was made. He was admitted to a local hospital on October 1, and had no respiratory difficulty while there. From October 1 to 7 he had urinary retention which was treated with an indwelling catheter. He was discharged to his home on October 15. He developed a cold, and was unable to cough well, but was unattended by a physician until October 28, when a diagnosis of right lower lobar pneumonia was made, and he was placed on sulfadiazine, 1 gm. every four hours. The drug was discontinued on October 30 because he developed hematuria. During his illness at home his temperature ranged from 101° to 103°F. He was admitted to the Poliomyelitis Service at Knickerbocker Hospital on November 1.

Physical Examination A 16 year old white boy who appeared acutely ill but in no respiratory distress. Respirations 28. Chest excursion was voluntarily limited because of pain on coughing. Cough was weak and deep breathing precipitated attacks of inadequate coughing.

Head Eyes and ears—negative. Mucous membranes of nose red and swollen. Pharynx red with a small amount of postnasal drip.

Neck 3 plus stiffness. Trachea in midline.

Chest No movement of intercostal muscles. Diaphragmatic movements appeared diminished but normal (clinical impression).

Heart Regular sinus rhythm, sounds of good quality. Rate 120. No murmurs heard. Point of maximal impulse in the 5th left interspace, 0.5 cm. within the midclavicular line (confirmed by three observers). Blood pressure not recorded.

Lungs Dullness over the right upper lobe, anteriorly, and flatness over right lower lobe posteriorly (? diaphragm). Diminished breath sounds over the right upper lobe anteriorly and absent breath sounds over the right lower lobe posteriorly. No rales of any type heard.

Abdomen Liver, spleen, kidneys not felt. Feces present in colon.

Genitalia Normal male.

Muscles Tightness of neck, back, hamstrings, gastrocnemii, soleus, quadriceps and pectorals. Weakness of both legs. Detailed muscle examination not made at this time.

Reflexes Absent knee jerks and ankle jerks bilaterally. Biceps, triceps and forearm reflexes active and equal bilaterally. Abdominals present in all four quadrants. Cremasterics active and equal.

Temperature 99.2° Pulse 120 Respirations 28

Laboratory Examination

Blood Admission count—hemoglobin 14.2 gm, red blood count 4.77, white blood count, 12,850, polymorphonuclears 66, lymphocytes 21.

Discharge count—hemoglobin 11.8, red blood count 4.02, white blood count, 6,500, polymorphonuclears 47, eosinophils 3, lymphocytes 50.

Kline and Kahn negative.

Nonprotein nitrogen 35 to 40 mg per 100 cc.

Blood sedimentation rate 30 (upper limits of normal 10).



Fig 83 (Case I) —Portable film taken one hour after symptoms of atelectasis. There is a nonhomogeneous density obscuring most of the right lung field, more marked over the lower lobe. Heart and mediastinum are drawn to the right. The right side of the diaphragm is not visualized.

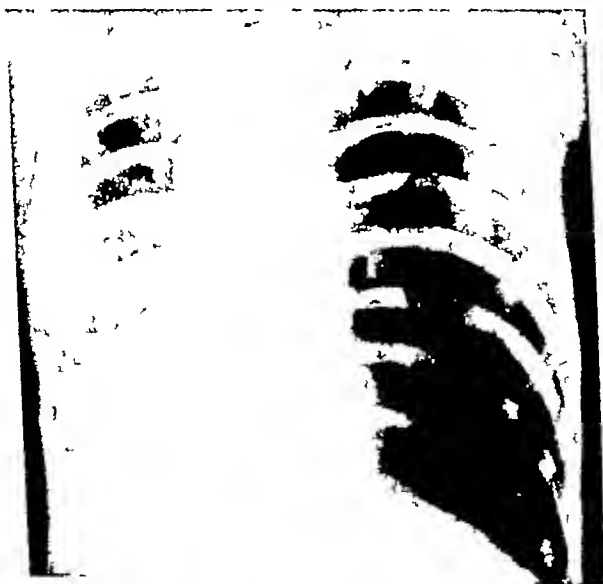


Fig 84 (Case I) —Film made seven days after atelectasis. There is definite clearing of the right lung field but the position of the heart and mediastinum remains unchanged. The right side of the diaphragm is revealed high.



Fig 85 (Case I) —Film made fourteen days after atelectasis The right lung field is clear but the position of the heart and diaphragm remains unchanged

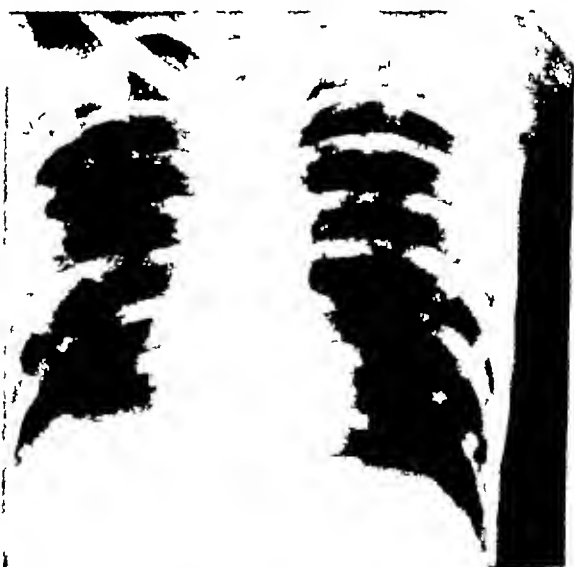


Fig 86 (Case I) —Film made fifteen days after atelectasis The heart and mediastinum have returned to a normal position Subsequent fluoroscopies showed gradual descent of the right side of the diaphragm and on January 10, 1940, both diaphragms were low in position

Urinalysis on admission showed red cells, casts, and 1 plus albumin. Red cells cleared in one week but fine granular casts persisted throughout hospital stay

Phenolsulfonethalein excretion test, 75 per cent of dye excreted.

Kidney concentration and dilution tests normal.

Electrocardiogram, no abnormalities

Vital capacity 3.6 liters

X-rays and fluoroscopies of chest—See Figures 83 to 86 X-ray of abdomen—no abnormalities, x-ray of spine showed slight dextroconvex scoliosis of the lumbar region

Course in Hospital On the afternoon of admission, the patient developed a sharp pain in the right chest with shift of the apical impulse to the left border of the sternum in the 4th left interspace. The patient was in mild shock. A diagnosis of atelectasis was made which was confirmed by x-ray, and symptomatic treatment of postural drainage and expectorants was begun, but the atelectasis remained unimproved.

Bronchoscopy was performed under ether anesthesia about forty-six hours after the development of the atelectasis and a large amount of mucus was aspirated from the right bronchus. The patient had been placed on penicillin on admission and this was continued for nine days. The highest temperature by rectum during this course was 99.8°. Ten days after the initial collapse, when the pneumonia had resolved, the lung re-expanded and the heart returned to its normal position. The right side of diaphragm remained high for two months.

The muscle status of the arms and legs was completely ignored until the chest pathology had cleared, and then the usual routine of physical therapy was begun. The rest of the course was uncomplicated, except for hematuria noted on admission which cleared in one week. Kidney function tests showed the kidneys to be in good condition but hypertension of 150/90 persisted, although asymptomatic.

On January 24, 1946, the patient was transferred to an orthopedic hospital. At that time the lungs and heart were perfectly normal but the patient was still unable to stand or walk.

CASE II

A 5 year old, white female was admitted on October 23, 1945, for treatment of poliomyelitis

Past History Noncontributory, except for frequent sore throats. These were relieved following a tonsillectomy and adenoidectomy at 4½ years of age.

Family History Mother, father, and three siblings living and well.

Present Illness The patient became ill on September 20, 1945, with general malaise, fever and vomiting on September 21, stiff neck on September 22. On September 23 she was taken to a local hospital and the diagnosis of poliomyelitis was made. Because of respiratory difficulty she was immediately placed in a respirator where she remained for two weeks. Except for the fact that she had muscle tightness and weakness in both arms, nothing more is known of her history. She was admitted to the Poliomyelitis Service of Knickerbocker Hospital on October 23, 1945.

Physical Examination. A small, frightened, 5 year old, white girl, breathing shallowly and irregularly. The intercostals and diaphragm appeared to be working, but were not synchronized. Temperature 99°. Pulse 90. Respirations 28.

Head Eyes, ears, nose and throat—negative. Tonsils out. Uvula moved in midline.

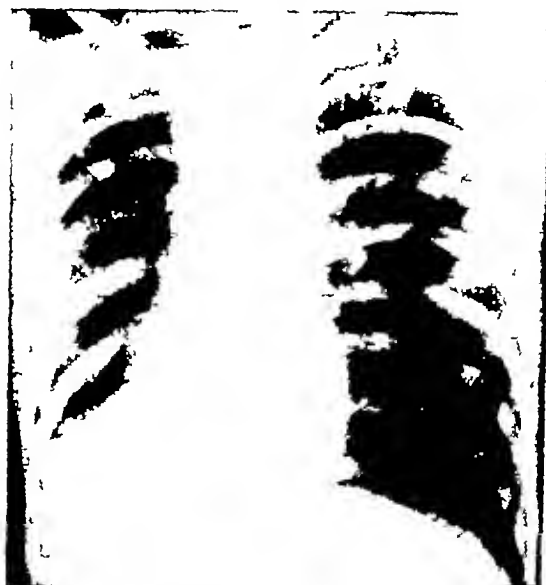


Fig 85 (Case I) —Film made fourteen days after atelectasis. The right lung field is clear but the position of the heart and diaphragm remains unchanged.

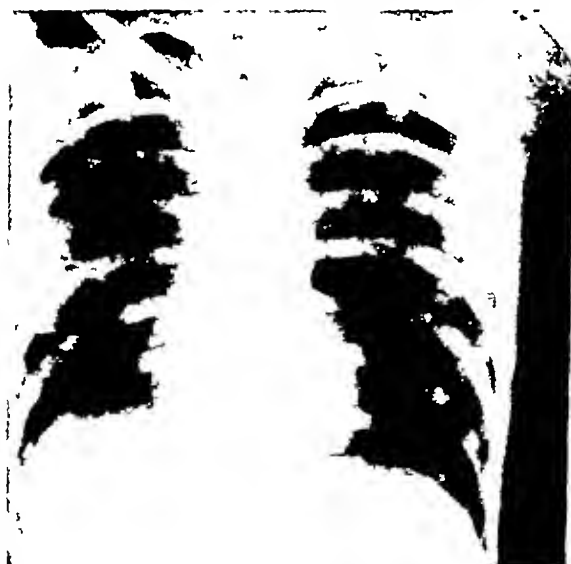


Fig 86 (Case I) —Film made fifteen days after atelectasis. The heart and mediastinum have returned to a normal position. Subsequent fluoroscopies showed gradual descent of the right side of the diaphragm and on January 10, 1948, both diaphragms were low in position.

Neck 1 plus stiffness Trachea in the midline
 Chest Heart not enlarged to percussion, rate 90
 Marked sinus arrhythmia. Sounds were of good quality No murmurs
 P₂ greater than A₂ Blood pressure 90/50
 Lungs clear to auscultation and percussion
 Abdomen Liver, spleen and kidneys not felt No masses or tenderness
 Genitalia Normal female
 Reflexes Left arm—absent biceps, triceps and forearm reflexes
 Right arm—all reflexes active and equal
 Legs—all reflexes active and equal.
 Abdominal reflexes—absent in all four quadrants



Fig 87 (Case II) —Portable film taken January 5, 1946 eight hours before death. Film shows an area of regional atelectasis in the right upper lobe with some shift of the trachea to the right.

Muscle Examination Accurate evaluation impossible, but tightness present in neck, back, hamstrings, gastrocnemii and pectorals. Weakness present in both left and right arms, and abdominal muscles. Legs—apparently normal strength.

Laboratory Examination.

Blood Admission count—hemoglobin 13.5 gm, red blood count 4.50, white blood count 8,000, polymorphonuclears 65, eosinophils 4, lymphocytes 30, monocytes 1.

Jan. 3, 1946—white blood count 10,500, polymorphonuclears 43, lymphocytes 57.

Jan 5, 1946—white blood count 10,000, polymorphonuclears 18, lymphocytes 52.

Blood serology negative

Sulfadiazine level Dec 17, 1945, 4 mg per 100 cc.

Urinalysis—constantly negative

X-ray of chest and fluoroscopy—see Figure 87

Course in the Hospital Because of a skin sensitivity to wool, for relief of muscle tightness the patient was placed on cold, wet cotton packs, rather than hot wool packs. Muscle tightness gradually improved. Respiration throughout her hospital stay never necessitated a respirator (except terminally) but any type of excitement would so upset her that her breathing became very irregular, rapid and shallow, though still adequate for her needs. When asleep, she seemed to breathe normally. Her course was uncomplicated until December 16, 1945, when she developed redness of the mucous membranes of the nose and throat and a few fine moist rales over the right upper lobe anteriorly without breath sound changes. The temperature was 102°F and a diagnosis of pneumonia was made and confirmed by x-ray. The patient was placed on sulfadiazine and the temperature receded to normal within twenty-four hours and remained so until January 6. The signs in the chest cleared and an x-ray confirmed the clinical findings of recovery. On January 4, she had a sudden attack of difficulty in breathing, without fever, and x-ray examination confirmed the diagnosis of atelectasis which had been suspected clinically. It became necessary to place her in a respirator immediately and sulfadiazine was started. Four hours after the onset of dyspnea, the temperature was 100°, but twenty-four hours later the temperature rose to 105° and the patient expired.

Autopsy Atelectasis of both right and left upper lobes, early focal bronchopneumonia, and acute gastric dilatation. In the brain there were small perivascular hemorrhages in the gray matter but no destruction of the Betz cells.

CASE III

A 12 year old, white boy was admitted on January 10, 1946, for treatment of poliomyelitis.

Past History Noncontributory

Family History Mother, father and six siblings living and well

Present Illness The onset of poliomyelitis was on July 11, 1944. The patient was taken to the Willard Parker Hospital where he developed a respiratory muscle paralysis complicated by bulbar involvement. All bulbar signs and symptoms cleared within four months, but the respiratory paralysis remained. At the end of six months he was transferred to another hospital, where he was gradually weaned from the respirator which he needed only for eating and sleeping. His stay there was uncomplicated until January 3, 1946, when he developed a fever accompanied by dullness, and diminished breath sounds over the left chest. A diagnosis of pneumonia was made and he again became completely dependent upon the respirator. He was immediately placed on penicillin. On January 10, 1946, he was transferred to the Poliomyelitis Service of Knickerbocker Hospital.

Physical Examination A pale, extremely emaciated, and acutely ill patient lying in a respirator in no acute distress. Color of lips slightly cyanotic.

Head Eyes, ears—negative. Mucous membrane of nose congested. Pharynx red with postnasal drip.

Neck 4 plus stiffness, neck circumference 8½ inches, trachea in the midline.

Chest Respirations rapid and chest cage pulled up as a whole by the neck muscles with marked development of the platysma muscle. No diaphragmatic activity noted.

Lungs clear on percussion but fine moist rales over left upper lobe anteriorly. No changes in breath sounds.

Heart Point of maximal impulse in the 5th left interspace, heart not

enlarged, sounds of good quality No murmurs Blood pressure 100/60

Abdomen Slightly distended Liver, spleen and kidneys not felt.

Extremities Both arms flail with absent reflexes Legs in good condition with deep reflexes active and equal.

Abdominal and cremasteric reflexes active and equal.

Temperature 100.6°F Weight 42 lbs

Laboratory Examination

Blood Admission specimen—hemoglobin 15 gm, red blood cells 4,28, leukocytes 20,750, polymorphonuclears 79, lymphocytes 29, monocytes 2, subsequent leukocyte count and differentials normal



Fig. 88 (Case III) —Portable film made January 14, 1946, four days after transfer to Knickerbocker Hospital. It revealed small areas of increased density at the left base and in the left hilar region with displacement of the mediastinum to the left. Subsequent x-rays showed clearing of these shadows and return of the heart to normal position.

Sedimentation rate remained elevated at 30 mm per hour

Nonprotein nitrogen 30 mg per 100 cc.

Blood serology negative

Urine Admission specimen showed 1 plus albumin and 20 to 30 red blood cells per high power field, subsequent urinalyses negative except for occasional casts

Electrocardiogram normal

Vital capacity 0.1 liters

X-rays and fluoroscopies of the chest—see Figure 88, x-ray of abdomen revealed a small calcium density (0.5 cm in diameter) in the pelvis of both kidneys

Course in the Hospital Penicillin therapy was continued, accompanied by supportive therapy. The signs of consolidation cleared clinically and by x-ray, but four days after admission another x-ray showed an atelectasis. There were no clinical signs to support this diagnosis. Twelve days after admission, penicillin was discontinued and the patient was taken out of the respirator for increasing periods of time.

Throughout the course, the highest temperature was 100.6°F. All chest signs cleared within twelve days and the patient's course was uneventful until April 2, 1946, when he developed a severe pain in the left lower quadrant of the abdomen and passed a small stone from the kidney pelvis to the bladder. These findings were confirmed by x-ray. Another small stone is, at present, in the right kidney, but the patient has been asymptomatic. Except for several attacks of air swallowing, which on two occasions resulted in enough respiratory distress to require the passage of a stomach tube with suction, the course has been otherwise uncomplicated. Physical therapy consisted of making the patient use his feet because his arms were completely useless, and he was discharged to a chronic disease hospital in September, 1946. At that time, he had learned to type and paint with his toes, but still could not feed himself.

CASE IV

A 6¼ year old, white boy was admitted on September 3, 1946, for treatment of poliomyelitis.



Fig. 89 (Case IV) —Portable film taken September 6, 1946, thirty-six hours after patient was put in a respirator. The film shows a dense shadow at the right apex and slight shift of the mediastinum to the right. Diagnosis: atelectasis of part of the right upper lobe.

eight hours after admission in those patients in whom improvement has been rapid enough to permit the patient to take the food by mouth. Actually in many severe cases food cannot be taken by mouth for one or two days and in such instances intravenous feeding, using dextrose solution, is necessary

8 Stimulants.—Patients unconscious for several hours, with low blood pressure and rapid weak pulse, may be given stimulants in the form of caffeine, epinephrine, ephedrine or transfusion. Actually the benefits from such medication seem to be temporary and slight.

9 Prevention of Coma.—Education and training of patients and physicians in methods for the control of diabetes and the correction of coma will accomplish more than its treatment. Patients need to know and carry out tests for sugar in the urine and some physicians find that the simple test for diacetic acid or acetone can be used without confusion and error by intelligent patients. The daily testing of urine and frequent submission of reports to the attending physician will result in the detection of early acidosis before symptoms have become serious. Patients must know how to give the insulin dose accurately and to adjust dosage for changing conditions. They need to weigh and measure food and know how to substitute one food for another, especially when traveling. Simple rules should be taught to all diabetic patients no matter how mild their condition seems in its early stages. Close contact with the family physician and careful reexamination at intervals has a further advantage that patients may have the advantage of new features of treatment.

PROGNOSIS

Important factors are (1) the severity of the acidosis, (2) the duration and degree of unconsciousness before treatment, (3) age of the patient, (4) the cardiorenal condition of the patient, (5) complicating conditions, and (6) grossly abnormal laboratory findings. The severity of the acidosis is a prime factor. Among 651 cases reported by Joslin and associates, there were eighty-five patients with a plasma carbon dioxide combining power or content of 5 volumes per cent or less and of these seventy-three recovered. It must be admitted, however, that some patients with higher values for carbon dioxide in the blood are fatal. In our Case I all the factors which ordinarily indicate a bad prognosis were present and yet recovery occurred even in the presence of severe infection and finally a major surgical operation. Rabinowitch has made use of a severity index of diabetic coma, rating the patient according to his age, duration of coma, presence

Past History Noncontributory except for tonsillectomy and adenoidectomy at four years of age

Family History Mother, father and two siblings living and well. Family history is positive for food allergies, asthma, and hay fever

Present Illness The onset of illness was on August 31, 1946, with headache, fever was present on September 1, when the patient was admitted to a Rhode Island hospital. On September 2 a stiff neck developed and a diagnosis of poliomyelitis was made. During this day he developed weakness of the right hand and was transferred to St. Luke's Hospital in New York City. On September 3 he developed weakness of the left arm and was admitted to the Poliomyelitis Service of Knickerbocker Hospital.



Fig. 90 (Case IV) —Portable film taken September 6, 1946, four hours after Figure 89, and about two hours after bronchoscopy with suction. The film shows clearing of the right upper lung field and a slight return of the mediastinum to the left.

Physical Examination A very apprehensive, white boy who appeared acutely ill.

Temperature 103° F, pulse 130, respirations 28

Head Eyes, ears, nose and throat—negative. Tonsils out.

Neck 4 plus stiffness, painful on motion.

Chest Respirations regular. Diaphragm and intercostals normal.

Heart not enlarged to percussion, rate 130, rhythm regular, no murmurs.

Blood pressure 118/82.

Lungs clear to auscultation and percussion.

Abdomen Liver, spleen and kidneys not felt. No masses or tenderness.

Genitalia Normal male.



Fig. 91 (Case IV)—Film taken December 14, 1946, because of extensive moist rhonchi. This shows an increase of both hilar shadows but not actual atelectasis.

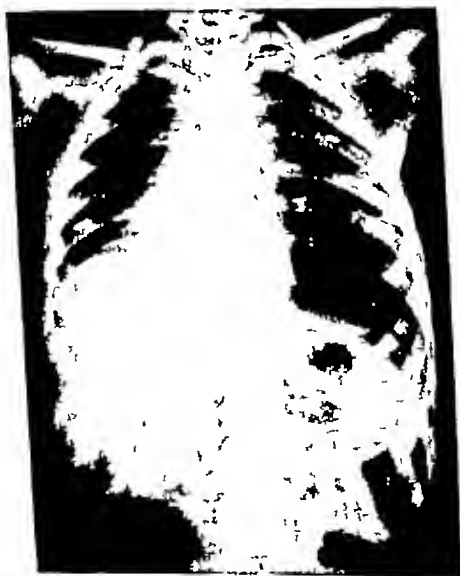


Fig. 92 (Case IV)—Portable film taken December 16, 1946, twenty-four hours after a prophylactic bronchoscopy. This film shows a small area of atelectasis at the right base, medially, with displacement of the mediastinum to the right and elevation of the right side of the diaphragm.

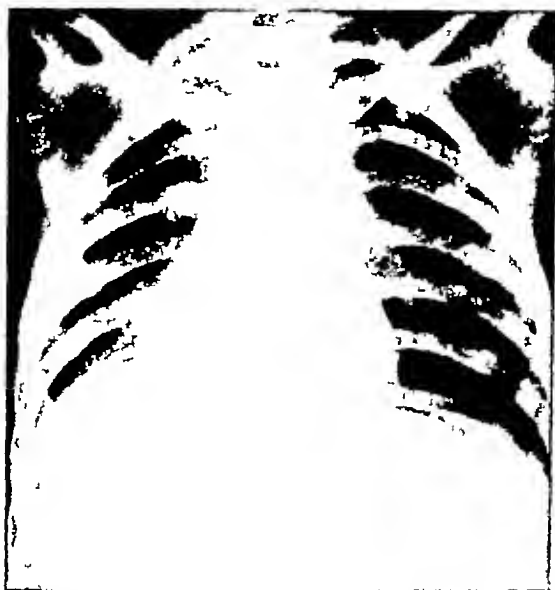


Fig 93 (Case IV) —Portable film taken December 17, 1946 This shows a slight return of the mediastinum to the left and a lowering of the right side of the diaphragm.



Fig 94 (Case IV) —Portable film taken December 19, 1946 This shows a new atelectasis of the right upper lobe (the patient's third) with marked shift of the mediastinum to the right. The right side of the diaphragm is again elevated.

Extremities Weakness of grip of both hands Legs in good condition Muscle tightness in neck, back and hamstrings

Neurological Lower extremities—ankle and knee jerks active and equal
Upper extremities—triceps on right absent, all other reflexes active and equal.

Cremasteric and abdominal reflexes active and equal.

Laboratory Examination

Blood Admission count—hemoglobin 13.8 gm (96 per cent), red blood cells 4.21, leukocytes 11,900, polymorphonuclears 72, lymphocytes 26, eosinophils 2

12/6/46—Leukocytes 19,450, polymorphonuclears 85, lymphocytes 14, basophils 1



Fig 95 (Case IV) —Portable film taken December 21, 1946, forty hours post-bronchoscopy This film shows complete clearing of the right upper lung field and return of the mediastinum almost to the midline

12/9/46—Leukocytes 22,450, polymorphonuclears 78, lymphocytes 21, basophils 1

12/16/46—Leukocytes 14,400, polymorphonuclears 80, lymphocytes 20

12/20/46—Leukocytes 10,300, polymorphonuclears 42, lymphocytes 55, eosinophils 3

12/23/46—Leukocytes, 8,950, polymorphonuclears 53, lymphocytes 40, eosinophils 3, monocytes 4

12/30/46—Hemoglobin 13.2 gm (92 per cent), red blood cells 310,000, leukocytes 9,400, polymorphonuclears 44, immature polymorphonuclears 1, lymphocytes 53, eosinophils 2.

Sedimentation rate 12/9/46—8 mm, 12/18/46—18 mm, 12/20/46—18 mm, 12/30/46—8 mm

Blood Kline and Kahn negative

Urinalyses consistently clear except for occasional casts

12/19/46—Culture from mouth and trachea, nonhemolytic streptococcus, culture from the right bronchus, nonhemolytic streptococcus, culture from the left bronchus, staphylococcus albus

Electrocardiogram 12/7/46—P-R interval 0.10 second, QRS 0.08 second, right axis deviation Electrocardiogram denotes right ventricular strain

12/18/46—P-R interval 0.14 second, QRS 0.08 second, right axis deviation Electrocardiogram denotes right ventricular strain.

Course in the Hospital On the morning of September 4, weakness of the right side of the diaphragm appeared, followed by weakness of the left side of the diaphragm and of the intercostals, so that it became necessary to place the patient in a respirator. Both arms were completely flail, and at this time penicillin intramuscularly and intravenously was started.

On the morning of September 8, in spite of his being in the respirator, it was necessary to give the patient oxygen because of marked cyanosis. A diagnosis of atelectasis was made although there were no abnormal signs in the chest. A portable chest film showed a collapse of the right upper lobe. A bronchoscopy, without anesthesia, was performed and the right bronchial tree aspirated. A portable film taken four hours later showed complete clearing of the atelectasis. The patient ran a febrile course from September 8 to 16 and his prognosis was doubtful, but then his condition improved remarkably and penicillin was discontinued on September 20. During the following weeks, he was gradually weaned from the respirator by day. However, the respirator was necessary for sleep.

Beginning on October 9, a mild pharyngitis was successfully treated for four days with penicillin lozenges. The patient's course was uncomplicated until December 6 when his temperature rose to 100° F. He vomited, became dyspneic and cyanotic, and was placed in the respirator full time. Because of gastric dilatation, aspiration by Levin tube was necessary. On the morning of December 7, he was placed on penicillin in spite of any physical signs to indicate an infection, and his temperature continued to range around 100° F. On the evening of December 7, for the first time, a few coarse rales were heard in the right anterior chest between the 3rd and 4th ribs. All chest signs disappeared, however, in the next two days and the patient improved somewhat except for the slight temperature elevation. On December 11, in spite of penicillin therapy, he developed loud, coarse rhonchi, especially in the right chest, and a fluoroscopy showed both lung fields to be well aerated. On December 15, in the hope of forestalling an atelectasis, a bronchoscopy was performed under topical pontocaine anesthesia and a large amount of mucus was aspirated from the right main bronchus. In spite of this, the patient developed an atelectasis of the right lower lobe on the next day, December 16, necessitating a second bronchoscopy. Postbronchoscopy films showed a clearing of the atelectasis. Because of redness of the bronchial mucosa, penicillin aerosol was given for a few days. On December 19, x-ray and physical findings indicated the development of an atelectasis of the right upper lobe and a third bronchoscopy was performed. A small amount of mucus was aspirated from the right bronchus and a large amount from the left. A film taken on December 21 showed clearing of the atelectasis of the right upper lobe. In spite of the unusual course which included four bronchoscopies, penicillin was discontinued on December 25 and the patient was afebrile and out of the respirator, enjoying his Christmas party.

COMMENT

In all four cases, the precipitating cause of the atelectasis was an infection of the respiratory tract. Penicillin and sulfadiazine have greatly aided the treatment of this phase. Only one patient (Case II) of the four died, but before the days of antibiotic treatment and chemotherapy, the case fatality rate would doubtless have been much higher. Case I illustrates the fact that the basic infection must be controlled if one expects to get the best results. Because of this fact, it has been our custom to treat with sulfadiazine or penicillin all minor upper respiratory infections as soon as they occur.

The temperature curve was formerly used as a differentiating factor between pneumonia and atelectasis—the curve of pneumonia being much higher than that of atelectasis. However, with the use of the sulfonamide drugs and penicillin, one can no longer rely on this. In case III pneumonia was definitely present but the highest temperature recorded was 100.4° (R).

All four patients were unable to cough. Two (Cases III and IV) could not cough because of paralyzed diaphragms, one (Case I) had a cough, but it was weak and ineffective because of weakness of the side of the diaphragm, and one (Case II) could not cough adequately, being apparently unable to coordinate her respiratory muscles and glottis. On fluoroscopy the diaphragm appeared to move normally.

Since all four patients were unable to cough up the secretions produced, one of two things had to happen to effect a cure: (1) their own body cells had to take care of the infection by phagocytosis and resorption of secretions or (2) the secretions had to be removed by mechanical means from the outside (bronchoscopy).

Two of the cases (Cases I and IV) responded well to bronchoscopy, and the life of one patient (Case II) might possibly have been saved had an immediate bronchoscopy been done. Also, the placing of this patient in a respirator may have involuntarily hastened her exodus, for the mucus which was already present in her upper respiratory tract was presumably sucked down into the lower respiratory tract. Because of her incoordination, it was absolutely necessary to give her some artificial means of respiration, but an attempt should also have been made to provide a clear airway. In Case III the patient recovered without bronchoscopy. The atelectasis was not evident clinically and was minimal on x-ray. It was associated with an infection of one week's duration. The boy was weak but seemed to be making satisfactory progress, and, therefore, we felt justified in waiting a day before advising bronchoscopy. His progress was satisfactory, and whether or not a bronchoscopy would have shortened the course is an unanswered question. On the other hand, in Case IV the patient was bronchoscoped before he acquired an actual atelectasis. This decision was taken because he had been filling up with mucus for three days.

and was unable to expel it. In spite of this "preventive" bronchoscopy, an atelectasis did develop.

All patients with poliomyelitis complicated by respiratory difficulty face the danger of a rapidly developing pneumonia. In addition, since they have very little oxygen reserve, when atelectasis occurs a bronchoscopy should be done as early as possible. With a patient who has a deficient oxygen supply, a few hours may mean the difference between life and death—for if the mucus is allowed to remain in the respiratory tract it will gradually cut down the oxygen supply by blocking off more and more of the lumen and cause more respiratory embarrassment. In order to insure the adequate removal of the mucus, bronchoscopy should be performed as often as is necessary.

In Case I the use of ether as an anesthetic may have been responsible for slowing the progress of the regression of the atelectasis, for ether is an irritant to the respiratory tract causing an increase in mucus production. Chevalier Jackson advises that bronchoscopy on children be done without either general or local anesthesia. However, in such cases sedation should be used. This method worked very well with three of the four bronchoscopies in Case IV. The administration of sodium phenobarbital intravenously just before the bronchoscopy was especially helpful in relaxing the glottis, and enabled the bronchoscopist to pass his instrument quickly and with little trauma.

Three of these cases (Cases II, III and IV) demonstrate the fact that an unusually low respiratory reserve is present in these patients, since it became necessary to place them again in the respirator day and night. Even though a patient has been out of a respirator each day for twelve to eighteen hours, when an atelectasis occurs, no matter how small, he may again become completely dependent upon the respirator. In such an instance, he should be left in the respirator until he feels that he is able to remain out, for it has been our experience that the patient is better able to judge his own oxygen reserve than the physician who must, of necessity, rely upon such signs as dyspnea and cyanosis. If a patient has been out of a respirator daily for two to four weeks, and then has to return to the respirator full time, one does not have to worry about his becoming "wedded to the machine." Normally, such a patient desires to get out and when his body tissues have received sufficient oxygenation, he will voluntarily release himself from dependence upon the respirator. Three of the very early symptoms of anoxia which are of advantage to the physician caring for such patients are headache, lightheadedness and slight dizziness.

The best treatment of atelectasis is *preventive*. The problem should be solved from two directions. First, protect the patient from respiratory infection. Exclude everyone who has a cold from coming in contact with the patient. The use of a mask by such contacts is not adequate. Second, treat every mild cold in a patient with respiratory diffi-

culty as though it were a beginning pneumonia. This usually means sulfonamide drugs or penicillin. Once the atelectasis has occurred, immediate bronchoscopy with suction should be used but even then the outcome is unpredictable.

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THERAPEUTIC EXERCISES IN PEDIATRICS

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INTEREST of pediatricians in muscle education and reeducation has been growing steadily until the majority are aware of the importance of therapeutic exercise as a valuable modality of treatment. At the same time, the importance of exercises as part of the education of the child and as a prophylactic is acknowledged. This paper attempts an over-all review of the field and at the same time a discussion of the common rationale of exercises.

Most pediatricians will be too busy to attend personally to the exercise treatment of their patients. This phase will usually be taken care of by physical therapists. Frequently, however, the pediatrician will have to advise treatment and will not be in a position to call on the services of a doctor specializing in physical medicine. Every pediatrician should know some facts about indications and the methods of exercise treatment. Exercise is indicated in most cases where the functioning of the muscle has been impaired.

Therapeutic exercises were introduced to this country by Dr G H Taylor with the publication of his book, "Exposition of the Swedish Movement Cure." While this book presents an over-all view of the various fields in which exercises are used, we are presently in a period of super-specialization. The trend to single out special systems of exercise therapy for special conditions is very much alive. It is deplorable that exercise therapy, which can be a valuable part of the therapeutic armamentarium, has been divided into a number of individual therapeutic fields (e g, posture work, cerebral palsy work, infantile paralysis work, traumatic work.) This branching off into different fields of exercise therapy has real drawbacks.

Physical therapists trained in only one of these fields will be less capable in others. They are prone to apply the principles of their own field to whatever problem they may encounter. They lose contact with the general problem of muscle development and the individual "systems" freeze, sacrificing the chance to improve and absorb new progress.

Furthermore, individual systems tend to develop "followers" with emotional, almost religious fervor, who swear by their adopted techniques.

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Far-reaching specialization may not be possible in small communities. A handful of persons, perhaps a single individual, may have to cope with the whole problem of muscle education in children and/or adults. Further, there is no planned program in effect to get constantly changing and developing information about physical therapy to a pediatrician.

COMMON DENOMINATORS

It has, therefore, been our aim to establish common denominators for exercise treatment and its prescription—common denominators which may serve as leads in the various fields of application of therapeutic exercise. We feel that an exercise prescription should be written and filled as accurately as any prescription for a highly potent drug. It should be based on proper analysis of the motor deficiency requiring treatment. This analysis should not only include indication of groups of muscles affected but the type of muscle deficiency requiring treatment.

Our analysis of muscle function will carry us only to a point where the elements found can be used directly as a basis for exercise prescription. Anything more complicated will lose its value as such basis. For a rough, working analysis it will be sufficient to differentiate three functional basic qualities of a muscle:

1. *Muscle Power*—the ability of the muscle to overcome resistance, lift or hold weights, based on its ability to contract.
2. *Elasticity*—the ability of the muscle to give up the state of contraction and actively adapt itself to varying lengths without straining its fibers.
3. *Coordination*—the correct play of muscle power (1) and elasticity (2) in the time unit.

We realize that these basic qualities are a gross oversimplification but they constitute the three main aspects of muscle action which can be directly translated into an exercise.

The leading principle for all exercise work is the fact that the muscle will develop exactly the quality which is called for in the performance of the exercise given.

If a muscle is called on to lift weights, to increase its contraction, its ability to contract and its power will be increased.

If a muscle is made to relax, to give up tenseness, to increase its length, its elasticity will be increased.

If a muscle is called upon to function properly in relation to other muscles, its coordination will be improved.

Another principle in prescribing therapeutic exercises is the fact

of coffee-grounds vomitus, complications such as infection, the plasma carbon dioxide and the blood pressure according to Table 5. Using this method Case I would have a severity index of 24 and the mortality in patients with this degree of severity is usually 83 per cent. One factor in the prognosis is the character of the preceding treatment and the closeness of contact between the patient and the physician who treats the coma. Thus Rabinowitz¹⁴ pointed out that in patients referred to him for treatment of diabetic coma whom he had not seen before, the mortality was 60 per cent, whereas in his own patients previously treated by him, the mortality for diabetic coma was less than 10 per cent. This is due not so much to the character of the diet as the fact that his own patients came to the hospital at an earlier stage in the coma than those patients coming from a distance and from other doctors. In our own experience, prognosis is chiefly affected by the promptness of treatment and the vigor of the treatment in the first two or three hours after the diagnosis is made. Thus, in our completely unconscious patients treated at the Deaconess Hospital the mortality has fallen from 35 per cent in cases treated prior to 1940 to only 10 per cent in cases treated since 1940, in spite of complications such as were present in Case 1.

SUMMARY

1 Two cases are described to illustrate (a) treatment of advanced coma complicated by pyelonephritis, bacteremia and amputation of the leg for gangrene and (b) hyperemia retinalis in pre-coma associated with low metabolic rate and insulin resistance.

2 The principles and methods employed in treating diabetic coma are outlined with emphasis upon (a) the reduction in mortality from 12 per cent to 2 per cent which occurred with increasing the amount of insulin given in the first three hours to an average of 215 units, and (b) administration of adequate saline solution to control dehydration loss of sodium and influence the anuria.

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that only sufficient repetition of a sufficiently difficult task will cause the muscle to increase whatever property is demanded of it. Let us call this requirement "exercise value." Since only a certain number of minutes every day will be available for exercise, it is vital to use all this time for necessary movements and to standardize these movements in order to concentrate on the muscles requiring treatment. It is also important in most cases to avoid fatigue and to avoid pain

INDIVIDUAL TYPES OF EXERCISES

1 Power.—The maximum weight which can be lifted by a muscle indicates its absolute muscle power. The length of time during which this weight can be lifted consecutively indicates the endurance. This period will be longer for weight that is less than the maximum capacity.

Exercises leading to muscle power are those which require the lifting of a weight or the overcoming of resistance. The weight may be represented by the weight, or partial weight, of the body region moved by the muscle. Whenever the muscle is too weak to manage the full weight of the body region, or whenever the synergists of a muscle are not able to give it adequate help, outward assistance has to be given to aid the movement. This may come through the supporting hands of a second person, through the buoyant effect of water in which the part is immersed or through the hands of the patient himself. Resistance to the muscle may be provided by some other person or by mechanical device.

The quantity of weight to be lifted, the resistance to the movement and the time of application must be increased gradually. Experiments registering the maximum weight-lifting capacity of normal persons have shown that the maximum weight that could be lifted was less on the second and third days than on the first. The fourth and fifth days brought a gradual increase. It took the subjects of the experiment approximately six days to a week to regain the weight-lifting capacity of the first day of training. From then on a gradual gain over the initial capacity was observed.

Power-building exercises should, therefore, begin on a gradually increasing scale so that the negative phase can be avoided. They should be continued regularly since doing them twice a week will barely maintain the status quo. As soon as the patient can return to his daily work, normal use will keep the muscle at the required level of efficiency. It must be emphasized, however, that unless the limb which has been treated is quite ready for normal use, there will always be a tendency on the part of the patient to favor it. In this case he will not find the necessary amount of exercise in his daily occupation and will lapse into a lower level of muscle power.

Overtaxing muscle power, especially in the initial stage of treatment, will result in discomfort and pain, not only in the affected muscles but often in affiliated muscle groups. Muscle spasm will set in or will be increased and limitation of motion will result.

2 Elasticity.—Elasticity can be diminished by impairment of a muscle's ability to actively release tension. This is the case in spasticity, painful muscle spasm as seen in acute trauma, or infantile paralysis. In this condition the first step toward a return to normal is symptomatic relief of pain. In spasticity (caused by lesion of the upper motor neuron) the muscle reacts with contraction to too many stimuli reaching it via the spinal cord. It does not relax when its antagonist contracts, but responds with contraction to the contraction of its antagonist. In this case, with no pain present, the first aim is relaxation.

Elasticity can be further diminished in a physical sense, the muscle having assumed a foreshortened length at its maximum relaxation. This state must be treated with active and/or passive stretching of the muscle contracture.

3 Coordination—Coordination is the well timed and well balanced functioning together of several muscles in a given movement. The function of a group of muscles is well balanced if the necessary degree of contraction is matched by an adequate degree of decontraction in the antagonists.

Normal movements of joints are produced by the concerted action of several muscles. These are made up of contractions of one group and decontractions of another. Changes of muscle length and tone occur in varying degrees. The simplest movement, therefore, constitutes a combination of many different muscle actions in several muscles and muscle groups. This constitutes a *movement pattern*.

In all previously described disturbances of muscle power and/or elasticity, the affected muscle will not be able to cooperate in a well timed and well balanced way with its synergists and antagonists. If its dysfunction is of minor degree, this disability may be hidden by other compensating muscles. When it is severe enough to be apparent it results in poor or lacking coordination—*incoordination*. This *incoordination* will be more obvious as the movement patterns become more complicated.

With power and elasticity perfect, coordination can still be impaired if timing and quantitative cooperation of some muscles are not functioning correctly. Lesions to the cortex, subcortex, spine and regulating afferent stimuli (tactility, balance and proprioceptive) are all possible causes for this malfunction.

If motor patterns cannot be established, or are forgotten, the symptoms of "incoordination" may be apparent. This is true physiologically when learning new skills.

PRACTICAL APPLICATION

After this broad general summary of the elements of therapeutic exercises we would like to demonstrate the practical application of the approach outlined. We have chosen for this purpose conditions that will be of special interest to pediatricians.

1 **Poor Posture.**—The large group of mild and moderately severe cases of poor posture require exercise treatment as well as severe cases needing such treatment before or after orthopedic procedure. We have found it helpful to use the following *structural measurements* as a basis for our exercise program.

- (a) The relative distance of the scapula from the spine
- (b) The level of scapulae measured with the water level.
- (c) Level of the anterior superior spine of the ilium
- (d) Length of legs
- (e) Angle of the pelvic tilt—protractor measurement.
- (f) Dorsal kyphosis and lumbar lordosis, gauged by measuring the relative distance from the plumb line to the 7th cervical vertebra and the 5th lumbar vertebra

These structural measurements do not give any direct lead for exercises but are merely indications of the present faulty alignment of structures. However, they help evaluate the following functional measures and thereby assist in establishing the basis of a program. The *functional measures* are

- (a) The circumference of the chest in medium position, deep inhalation and maximum expiration
- (b) The total elasticity of the pectoral muscles, measured by the angle to which arms can be passively elevated in a vertical direction
- (c) The elasticity of the hamstrings, measured by the angle at which the legs may be lifted passively from the supine position without causing motion in the lumbar spine
- (d) The total elasticity of hamstrings and back muscles, measured by the ability to touch the floor with the fingers of both hands by bending over, knees completely straight
- (e) Muscle power of abdominal muscles, measured by the child's ability to raise both straight legs to an angle of 45 degrees and keep them there to the count of ten
- (f) Strength of the upper back muscles, measured by the ability of the child to raise his trunk over the edge of a table and hold it to the count of ten
- (g) Strength of lower back muscles, tested by having the child raise his pelvis over the edge of the table and remain in a horizontal position to the count of ten

Depending on the location of the deficiency, the child may be given special strengthening to lower or upper abdominal muscles or special stretching for pectorals or hamstrings. If unilateral deviations are noted in the structural measurements, the strength and elasticity of the left

and right trunk muscles are tested individually and strengthened or stretched respectively

Breathing deficiencies, as demonstrated by too small an inspiration or overexpiration, are treated with appropriate breathing exercises

Patients with deficiencies such as relaxed arches, pronated heels, weak anterior tibials and foreshortened calves or peroneal muscles are given exercises for specific deficiencies (not simply a general series of foot exercises for all "foot trouble")

Once the functional deficiencies have been corrected and the child can actively assume, and easily hold, the best position permitted by possible structural deformities, we proceed to teach the use of the acquired good muscle function by "habit training" Frequently this habit training is unnecessary, the child assuming the proper posture habit as soon as the functional basis for it has been established

By this approach we avoid fitting the child into any one of the numerous "systems" but utilize whatever exercises are necessary for the individual case

2 Infantile Paralysis.—This condition has been especially fertile in the production of systems and emotional followers of them It is unnecessary to state that muscle reeducation is an important part, but only one part, of over-all treatment Unfortunately, this symptomatic treatment has been overemphasized We share the belief that in the not too distant future the treatment of infantile paralysis with muscle reeducation will yield to causative and preventive treatment

Here, too, the treatment of (a) deficiency of muscle power, (b) deficiency of muscle elasticity (spasm and contracture) and (c) poor coordination, are sufficient basis for a rational approach

(a) *Deficiency of Muscle Power*—In the acute stage the main attention is given to relief of pain and spasm and the prevention of contractures However, muscle power should be preserved as much as possible. The general rule "Watch pain limit and fatigue limit" must be most carefully adhered to All weak muscles (we dispense with the description of the generally known muscle grading and charting) should be made to work for a short time, possibly two or three times daily The work given in this acute stage will be far below the fatigue limit and will consist of guided motion if necessary and assisted motion through the full range possible without producing pain

As soon as acute symptoms and pain are relieved, the dosage should be increased Resistance should be applied to all muscles that can take it and antigravity exercises weakly given to all muscles able to perform them It is a definite and frequently made mistake to keep too far below the fatigue limit and not give sufficient exercise value to weak muscles

At this stage, and far into the chronic stage, stimulating massage

and galvanic motor point stimulation should be added to power-building exercises

In the chronic stage, power-building exercises should be concentrated on muscles capable of improvement and a steady increase of dosage maintained. At the same time, the exercise periods should be increased. The most common mistake in the chronic stage is under-exercise.

A word may be added on the technic of giving power-building exercises. We feel that the use of established movement patterns is much more helpful than the attempt to create unusual ones.

The order "touch here" given with the toes of the child directed toward the fingers of the therapist will produce the proper type of dorsiflexion of the foot easier than the order "tighten here" or "pull here" with the fingers of the therapist pointing to the anterior tibial muscle. Few normal people are capable of contracting individual muscle groups at will. We have been trained to use our muscles with the aim of producing action rather than with the thought of tensing or relaxing individual groups.

(b) *Elasticity*—In the acute stage, muscle spasm and pain are the main symptoms to be dealt with. Hot baths, hot packs and, of late, certain drugs have been successfully used for this purpose. Proper positioning is an added means of relieving painful muscle spasm and preventing contracture. As soon as this acute stage is over the prevention of contractures and treatment of what contractures may be present is started.

The first and most gentle procedure is the reflex stretch, performed by giving resistance to the antagonist of a contracted muscle, thereby causing reflex relaxation.

The next step is active stretching, in which the child himself stretches a foreshortened muscle (such as stretching a calf muscle) by forced active pulling of the muscle by contraction of its antagonist.

(c) *Coordination*—The teaching of coordination should be reserved for the chronic stage when it is evident that the use of certain muscles has been permanently impaired and the problem of adjustment arises. It is expedient to concentrate on power and elasticity as prerequisites to coordination. Quite frequently coordination follows spontaneously after restoring these two qualities.

3 *Cerebral Palsy*.—In this group of conditions, as in any of the others, we must remain aware of the fact that exercise (motor training) is only one of the many treatment modalities and measures required for satisfactory results. It is more obvious here than in any other condition that the striated muscle is our only means of expression. Since the ability to speak, write, move the facial muscles, or motion, may be impaired, the treatment of these respective muscles

will improve the patient's ability to express himself. Thus, a seemingly retarded child may gradually emerge as normal or even of advanced intelligence.

As commonly known, there are three major groups of cerebral palsy of which the respective leading symptoms are spasticity, ataxia and athetosis. We will confine our discussion to spasticity.

(a) *Power*—In spasticity the muscle analysis will determine the loss of power, if any, and its distribution. Sometimes certain muscles may be normally strong but entirely without function. They may be made to function in an unexplained and indirect way. Dorsiflexion of the foot, for instance, may be caused by giving resistance to lifting of the flexed knee. (This phenomenon is called "confusion") The exercises given to increase muscle power may utilize this confusion. If a child is old enough, resistance and antigravity exercises may be used in muscles responding to volition.

(b) *Elasticity*—The exaggerated reaction of a muscle to all stimuli, causing spasticity, is the main and more obvious problem in this group of cases. The spastic muscles should be graded (i.e., 1 plus, 2 plus and 3 plus) and their distribution charted. This is necessary to direct the exercises to the parts that most require them.

The exercise aim is relaxation of the muscle. In congenital cases (the majority) treatment will at the same time aim at the establishing of movement patterns which have not been formed in the child and at reciprocation if absent.

Conditioning exercises consist of passive rhythmic movements performed with the aim of eliciting spontaneous repetition by the child. In order to produce this spontaneous repetition, or at least active participation by the child, these rhythmic movements are frequently performed together with the singing of nursery rhymes. Either power or relaxation is stressed, depending on which is desired.

In secondary hemiplegias, such as seen after encephalitis, the approach is slightly different. Here, in most cases, movement patterns have been performed but have been obliterated by the upper motor neuron lesion. In the majority of these cases the primary aim will be to prevent spasticity and, if the child is old enough, active or conscious relaxation will be stressed. The patient will be taught the difference between a tight and a relaxed muscle and will gradually learn how to suppress tightening of a muscle while at rest, later when receiving passive movements and still later when doing active movements himself.

This approach, with conscious relaxation, will be useful in older age groups of patients with congenital cerebral palsy as well, but since movement patterns have not been previously performed it will only be useful at a much later stage than in secondary brain injuries. On

the other hand, very young children with secondary hemiplegia may not be capable of conscious relaxation and will require conditioning exercises

Contracted muscles must be stretched passively since they do not yield to relaxing exercises.

(c) *Coordination*—Part of the treatment will be the teaching of skills such as ski-walking, walking in the walker and the important field of occupational therapy for the upper extremities. The use of occupational therapy for the establishment of the leading hand should precede actual exercises in order to avoid speech difficulties or seizures. Occupational therapy remains the most vital modality in the treatment of the upper extremities.

Speech training, too, is based on exercises with the aim of establishing certain lacking tongue motion. When this is secured, speech training on a higher level is added in cases with defects of the speech center.

Treatment of the other types of cerebral palsy, as well as a large number of other conditions requiring exercises, cannot be discussed in this limited space. We would like, however, to at least enumerate the following important groups in which exercises are indicated: torticollis, Erb's palsy and other lesions of the motor nerves, arthritis, asthma and, last but by no means least, cardiac conditions. This latter group, too, may be greatly benefited by gradual and planned muscle education.

The importance of proper feeding, sunlight, climatic conditions and so forth have been fully recognized, but the importance of muscle education has still to come into its own. When admitted to its proper place, it will play an important part not only in curative but in preventive treatment.

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THE NEWER CONCEPTS IN THE MANAGEMENT OF SYPHILIS IN CHILDREN

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I. THE USE OF PENICILLIN ALONE

THIS discussion of the treatment of congenital, as well as acquired, syphilis in children will be limited to the use of penicillin alone

While the reports in the literature are still scarce on the use of penicillin in the treatment of syphilitic disease in children, enough time has elapsed for a report to be made on the methods, choice of drug and final results

PROPHYLACTIC TREATMENT OF THE SYPHILITIC PREGNANT WOMAN

The prophylactic treatment of the syphilitic pregnant woman is of the utmost importance in eradicating congenital lues. The material gathered by Ingraham¹ and his associates, as well as by Goodwin and Moore,² gives us enough information to permit an evaluation of sodium penicillin in the prevention of prenatal syphilis. The cases chosen by these authors, especially by Goodwin and Moore, consist of patients who had lesions of early syphilis. This limitation of clinical material, in the words of these authors, was undertaken primarily for the purpose of evaluation of penicillin because of (1) the practical certainty of infection of a fetus born of a mother with outspoken syphilis and (2) the lack of such certainty in infants born of mothers with latent syphilis. This is certainly true, since it is a known fact that mothers with latent syphilis may give birth to nonsyphilitic infants.

The Dosage of Penicillin in Pregnant Women.—The average dosage consists of 2.4 million units. It may be given either in three-hour doses for 120 doses equally divided, or the doses can be divided as follows:

- (1) 10,000 Oxford units sodium penicillin intramuscularly every three hours for eight doses, followed by
- (2) 20,000 Oxford units sodium penicillin intramuscularly every three hours for eight doses, followed by
- (3) 40,000 Oxford units sodium penicillin intramuscularly every three hours for fifty-four doses

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The penicillin is administered intramuscularly in aqueous or saline solution at intervals of between two or three hours night and day. The duration of the treatment should be somewhere between ten and fourteen days.

Primarily we are interested in the woman giving birth to a normal infant, and from all reports in the literature we can safely say that with this method of treatment a normal nonsyphilitic child can be born. The newborn infant should be observed for at least six months, the Kahn titer taken regularly and an examination of the long bones should be done at least once or twice.

In the Genitoinfectious Disease Clinic Dr. Albert Heyman found that in a series of six pregnant women with secondary syphilis, every child born so far has been negative for syphilis and the Kahn has remained negative. The following case will serve as an illustration.

H. T., SYPHILIS, SECONDARY, EARLY TREATED WITH 24 MILLION UNITS OF PENICILLIN NINE MONTHS PREGNANT. ADMISSION DATE 6/8/45

	Kahn Titers	Child born	Kahn Titers
6/8/45	160	7/7/45	7/6/45
7/7/45	40	9/18/45	3
9/8/45	0	10/8/45	Doubtful
10/8/45	0	11/27/45	0
11/5/45	0	12/22/45	0
12/22/45	0	11/1/46	0
11/1/46	0		0

Mothers whose titers show relapse during pregnancy should receive another complete treatment of at least 48 million Oxford units of sodium penicillin intramuscularly.

Normal infants can be born to pregnant women who were treated during the first pregnancy for secondary syphilis, but failed to receive any treatment during their second pregnancy. This has been demonstrated by Ingraham and his workers in a case in which both children were born normal.

It is not my desire to discuss the final effects of penicillin on the disease in the mother, but I think one can be impressed with the value of the use of penicillin in the prevention of congenital syphilis, as only on rare occasions do we find a syphilitic infant born of a pregnant woman treated with penicillin, nor can we presume that penicillin is the cause of abortion in a syphilitic pregnant woman.

While arsenical and bismuth therapy must be instituted very early in pregnancy and may result in marked toxicity to the patient, penicillin, on the other hand, may be used relatively late in pregnancy with little toxic effects on the mother or child, and with an excellent chance for delivery of a normal infant born of a syphilitic mother.

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TREATMENT OF CONGENITAL SYPHILIS

There are still but few, meager reports available regarding the value of penicillin in the treatment of congenital lues. There are also many manifestations found in congenital syphilis which are predominantly present only in this infection. The treatment of each one will be discussed individually. All the reports up to this date are confined to children treated with commercial penicillin. We have had the opportunity of using crystalline G penicillin, but have not sufficient data to report results obtained from its use. The commercial penicillin has so far contained an unknown amount of the fractions G, F, X and K. These fractions have varied from time to time, and for that reason one can suspect that the change in these fractions had a definite effect on the therapeutic efficacy, which may have not remained constant. We believe, however, that in the future this will be corrected and one may adhere to the use of crystalline penicillin.

The Dosage of Penicillin.—Crystalline sodium penicillin G can be given in the dosage from 80,000 to 100,000 units per kilogram of body weight. It is dissolved in isotonic saline solution and given intramuscularly every two or three hours for a period of ten to fourteen days. While gradually increasing doses of penicillin can be given from the first to third day, our experience has shown that no better results are obtained than when the penicillin is given in equally divided doses for the period of time stated above. Sodium penicillin is used alone, no further antisyphilitic treatment being given.

Serologic titers are made at monthly intervals. These patients should be observed for several months at monthly intervals, and after the first year, at least every six months for several years.

Spinal fluid examinations should be done if there is any evidence of neurologic involvement, and if a relapse occurs during the penicillin treatment. All patients, however, should have a spinal fluid examination at the end of the observation period and at the end of the first year.

Roentgen rays of the long bones should be taken at intervals following the treatment, and should be compared with the first examination. The roentgen ray examination, however, is not done routinely in acquired syphilis, as in infantile congenital syphilis, unless one has a reason to suspect some luetic lesions of the bones in either latent or acquired syphilis.

Reactions.—Very few toxic effects are seen from the use of sodium penicillin in the treatment of congenital syphilis. In fact, in our experience only two reactions were seen. (1) The Herxheimer reaction occurred in a great number of cases. These reactions manifest themselves by elevations of temperature to anywhere between 100 and 105° F. The hyperpyrexia usually persists for one to one and a half days. From our experience it seems that no injurious effects to the child

are seen as a result of this reaction, and penicillin may be continued with impunity during the period of this reaction and following it. It was thought at one time that this reaction might be due to the fact that the penicillin was given in equally divided doses, but in a number of cases in which the penicillin was gradually increased up to the third day the same reaction was seen (2) Occasionally a rise in the serologic titer is seen during the administration of penicillin. This increase is only transient and apparently is another manifestation of the Herxheimer reaction, and for that reason should not be disturbing to the physician.

Serologic Reversal.—In infantile congenital syphilis, especially in patients who are under 4 months of age, the reversal of the Kahn titer usually occurs over a period of three to six months after the completion of penicillin therapy. The duration of infection plays a definite part in serologic reversal and it may be said, the younger the child, the shorter the infection and the quicker the reversal to normal. The usual period of reversal in a young child is anywhere from three to six months. However, in a number of cases in which the initial Kahn is high, the period of complete reversal of the Kahn titer may take from nine to ten months following penicillin therapy. In acquired syphilis the serologic reversal may sometimes be delayed. In our cases of acquired syphilis that have been followed for about six months, two patients became negative during that time, but in the other five a definite fall in the serologic titer was noted from month to month.

Serologic Relapse.—Serologic relapse is uncommon in young infants affected with congenital lues and the dosage of penicillin does not seem to have the direct effect on the change in Kahn titer. One of our patients recently reported in the literature was treated with 42,000 units of penicillin per kilogram of body weight. Although the quantitative Kahn titer had fallen from 400 to 80 U in six weeks, it rose in five months to 640 U. Re-treatment with double the original amount of penicillin was instituted and five months later the serologic titer was 4 U and the spinal fluid was normal, whereas the spinal fluid at the time of the relapse revealed 56 cells, 54 mg of protein per 100 cubic centimeters and a positive Wassermann test with 0.125 cc of fluid.

While spinal fluid examinations are usually made at the onset of the disease, it is of the utmost importance to make one when a serologic relapse occurs, as we have found in our relapse cases a spinal fluid which presents some inflammatory process.

General Clinical Response.—Only the results in infantile congenital syphilis can be discussed under this heading, as the lesions of early infantile congenital syphilis differ greatly from those of the latent lues. The majority of these patients present definite cutaneous and

mucosal lesions, chronic pharyngitis and superficial ulcerations with bleeding. Enlargement of liver and spleen is seen in a great majority of cases. Many osseous lesions, especially pseudoparalysis, are seen at this stage. All lesions except the osseous lesions respond immediately and usually disappear before the end of penicillin therapy, so that by the end of the course of treatment all skin and mucosal lesions can hardly be demonstrated in the infant.

Roentgen ray examination shows a slight improvement of the bone lesions during the treatment and immediately following the treatment, but in most cases these lesions usually clear in about three to six months after penicillin therapy. Occasionally osseous syphilis may show spontaneous improvement without treatment, as many patients treated for the first time will submit a roentgen ray report of healing syphilis, but these lesions will certainly heal more rapidly after the use of penicillin.

Seroresistance.—It is a well known fact that under all conditions and during all kinds of antisyphilitic treatments a certain number of children will continue to show persistent positive serologic reactions of the blood many months after treatment. If these children continue to have a normal spinal fluid and fail to demonstrate any lesions of luetic character, but still continue to have a persistently low serologic titer, they should not, under any ordinary circumstances, be subjected to any further antiluetic treatment. These patients, however, should be watched carefully for many years.

Deaths.—Occasionally death will occur in some young infants during the penicillin therapy. Platou,³ Heyman and Yampolsky,⁴ and Yampolsky and Heyman⁵ have observed a few deaths in such cases. The question usually arises whether penicillin therapy alone can produce such fatalities. It is interesting to know that during the treatment of these cases there may be some evidence of healing, especially in bone lesions, but because of either prematurity or the extensiveness of damage which occurred before treatment was begun, these patients will die in spite of the penicillin therapy. Heyman and Yampolsky conclude, "The greatest factors in the prevention of death from congenital syphilis are—adequate nutrition and hydration, and the prevention of intercurrent infections." Since deaths of children with congenital syphilis cannot be prevented by the treatment of syphilis, it must be remembered that the majority of fatalities in these patients occur among severely infected infants who are premature and malnourished.

THE RESULT OF TREATMENT OF INTERSTITIAL KERATITIS

This condition has been most difficult to treat with arsenical and bismuth preparations, and apparently is not amenable to penicillin therapy. Occasionally some effectiveness may be seen, but as a rule

the circumcorneal congestion and corneal opacity remain. The serologic titers may fall somewhat, but we have observed no serologic reversal. Even with instillation of penicillin solution locally there seems to be no improvement as the result of this treatment. It is suggested that the penicillin therapy alone be abandoned in the treatment of interstitial keratitis. Fever therapy, combined with penicillin, or other methods should be instituted immediately in the hopes of prevention of complete opacity of the cornea.

CLUTTON'S JOINTS

The use of penicillin in symmetric hydroarthrosis has failed to show definite improvement. There seems to be little response and effusion may remain for months after treatment. In one of our cases reported recently, during the treatment of Clutton's joints, there developed an interstitial keratitis in the same patient.

CONGENITAL NEUROSYPHILIS

Stokes, O'Leary⁶ and others have reported excellent response in changes in the spinal fluid with the use of penicillin therapy in adults. Our experience has been limited to three conditions—*asymptomatic neurosyphilis* and *paresis* in congenital lues, as well as *progressive eighth nerve deafness*. The great majority of patients with *asymptomatic neurosyphilis* showed group III findings, with a definite strongly positive Wassermann, and elevation in cell count, protein level and the mastic curve reaction. These patients, as a whole, have shown marked improvement, and certainly as good an improvement as seen after fever therapy. Although the Wassermann test in these patients remains positive there is some reduction in the titer. There is also reduction in cell count as shown by the following chart, which compares the treatment of *asymptomatic neurosyphilis* with penicillin and fever therapy.

RESPONSE OF CEREBROSPINAL FLUID TO PENICILLIN COMPARED WITH FEVER THERAPY—ONE AND A HALF YEARS OBSERVATION

<i>Penicillin</i>			
Cells	Prot	Mastic	Wass
39	85	444431	44444
0	32	000000	44400
<i>Fever</i>			
70	48	444432	44441
0	31	000000	44100

Juvenile paresis, with the treatment of penicillin alone, does not display much clinical change but the spinal fluid may show some improvement. These cases may be treated with penicillin, but fever

therapy should be instituted at the same time, as little benefit can be obtained with penicillin alone

Severe eighth nerve deafness does not respond to the treatment of penicillin alone, as can be demonstrated by an audiogram

SUMMARY

In outlining the treatment consisting of penicillin alone, the subject may be divided into two categories

1. Infantile Congenital Syphilis and Acquired Syphilis in the Young

(a) *Prophylaxis*—The value of penicillin in the treatment of the pregnant syphilitic woman has been definitely established. A dosage of 24 million units for a period of about ten days should be given every syphilitic woman as soon as one is satisfied of the diagnosis of this condition. If a relapse occurs, re-treatment with double the dose of the penicillin should be given. While it is suggested that no re-treatment is necessary during a second pregnancy in a woman who has been treated for secondary syphilis during her first pregnancy, I believe one should be cautious and should consider seriously repeating penicillin therapy in every syphilitic mother.

(b) At least 100,000 units of crystalline penicillin per kilogram of body weight should be given in every case of early infantile congenital syphilis. Administration should be by the intramuscular route every two or three hours for a period of ten days. The Herxheimer reaction may be disregarded, as it has no influence on the toxicity or the delay of the treatment of the infant. Serologic relapse is a warning that penicillin therapy must be repeated, with the dose at least doubled. Spinal punctures are indicated in all cases of relapse and at the end of a year's follow-up of the well patient. Roentgen ray study of all long bones should be made at the beginning of treatment and repeated at intervals until complete healing is demonstrated. The patient should be watched carefully for late manifestations of syphilis.

2. Late Congenital Syphilis and Neurosyphilis

(a) The two outstanding conditions found during this period are interstitial keratitis and Clutton's joints. Neither one of these conditions responds favorably to penicillin therapy, and other methods, such as fever therapy, should be used in the treatment of interstitial keratitis.

(b) Asymptomatic neurosyphilis shows some response to penicillin alone. It is possible that in this condition, as well as in juvenile paresis, the addition of fever therapy will bring about better response and a greater improvement, not only clinically but also serologically.

(c) Progressive eighth nerve deafness in our experience shows very little improvement under penicillin therapy.

CONCLUSION

In general it may be said that early infantile congenital syphilis, as well as acquired syphilis, will respond to penicillin therapy as well as to bismuth and arsenical therapy. The duration of treatment and the immediate response certainly should favor the use of penicillin in all these cases.

It is possible that larger doses of crystalline penicillin, up to 200,000 units per kilogram of body weight, will be necessary in the future to bring about complete healing of the young syphilitic infant.

II SUGGESTED TREATMENT IN SERORELAPSING AND SERORESISTANT PATIENTS WHO DO NOT RESPOND TO PENICILLIN TREATMENT

O'Leary and others have suggested the use of small frequent doses of mapharsen during the penicillin treatment. It is presumed that better results may be obtained in this manner. A short course of bismuth may also be given to these patients in the hope that the quantitative titer can be lowered or reduced to zero. It is my own opinion that when these patients do not respond to full doses of crystalline penicillin the old methods should be used in full courses in order to obtain better results. The following methods are suggested.

Acetarsonic Alone and Combined with Bismuth Salicylate.—Acetarsonic contains from 27.1 to 27.4 per cent of arsenic and is chemically known as acetylaminohydroxyphenylarsonic acid. A 0.25 gm tablet contains approximately 0.0068 gm of arsenic while a 0.1 gm tablet contains approximately 0.0027 gm of arsenic. A course of treatment is shown in the following table.

Period	Duration of Period	Dose of Acetarsonic Daily per Kg
First	7 days	0.005 gm ($\frac{1}{20}$ grain)
Second	7 days	0.010 gm ($\frac{1}{10}$ grain)
Third	7 days	0.015 gm. ($\frac{1}{8}$ grain)
Fourth	7 days	0.02 gm ($\frac{1}{5}$ grain)
Fifth	5 weeks (5th, 6th, 7th, 8th, 9th weeks)	0.02 gm ($\frac{1}{5}$ grain)
Sixth	6 weeks	None (rest for 6 weeks)

Duration of entire active course, 9 weeks

This medication can be made up in powder and given either in daily doses once daily, or in three doses given about six hours apart. Acetarsonic can be mixed in milk and given about one-half hour before meals. It decomposes rapidly in an acid medium.

Certain reactions may occasionally be seen following the use of this drug: (1) eruption of scaly nature over the body, (2) diarrhea, (3) hyperpyrexia, (4) pyuria, (5) nephritis and (6) flaccid paralysis. We

have had no instance of flaccid paralysis in our experience, but this complication should be watched for. However, when all the other complications are present the drug may merely be discontinued for a few days and as soon as the complications clear up its use may be resumed.

Two methods of treatment with acetarsone and bismuth are outlined here.

1 *Early Congenital Syphilis*—The course consists of seventy-five weeks of treatment, alternating nine week courses of acetarsone and six weeks' course weekly of bismuth injections for five consecutive periods of fifteen weeks each. That means, nine weeks of acetarsone followed by six weeks of bismuth.

2 *Late Congenital Syphilis*—Seventy-two weeks of acetarsone, using acetarsone daily and dividing it into eight periods. This is done in order that the acetarsone may be used gradually up to the highest number of grams and then resumed again at the end of nine weeks with beginning of small doses. Once a week these patients are given an injection of bismuth. That means, each patient receives seventy-two injections of bismuth and seventy-two full weeks of the use of acetarsone.

The results many times are gratifying and a serologic reversal may be obtained in many cases.

If arsenicals are desirable, then a full course of treatment, combined with bismuth, is advisable as outlined in the following chart.

Duration	Drug	Dosage	Remarks
1 to 6 weeks	Neoarsphenamine	0.1 gm. per 15 lbs body wt	
	Sulfarsphenamine	0.1 gm per 15 lbs body wt	
	Mapharsen	0.75—1.00 mg per kilo body wt	
6 to 12 weeks	Bismuth subcylate in oil	$\frac{1}{2}$ gr per 20 lbs body wt.	Kahn taken
12 to 18 weeks	Arsenical preparations	Same	Kahn taken
18 to 26 weeks	Bismuth subcylate in oil	Same	
26 to 32 weeks	Arsenical preparations	Same	
32 to 42 weeks	Bismuth subcylate in oil	Same	Kahn taken
42 to 48 weeks	Arsenical preparations	Same	
48 to 60 weeks	Bismuth subcylate in oil	Same	
60 to 65 weeks	Arsenical preparations	Same	Kahn and spinal fluid examination taken
65 to 80 weeks	Bismuth subcylate in oil	Same	

After eighty weeks of treatment discontinue treatment, see patient from time to time for six months and then follow up patient to puberty.

While mapharsen has been used to a great extent in the treatment of adult syphilis, it is always desirable to have a drug which can be used intramuscularly in case the intravenous therapy presents difficulties, especially in very young infants. For that reason, we can suggest the use of nearsphenamine or sulfarsphenamine which can be given intramuscularly in the dose of 0.1 gm. to 1 cc. of distilled water, half of the dose being given in each buttock.

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THE TREATMENT AND PREVENTION OF ROCKY MOUNTAIN SPOTTED FEVER IN CHILDREN

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INTEREST in Rocky Mountain spotted fever has increased during the last five years because of the several advances that have been made in the study of this disease and the other rickettsial diseases affecting man. It has been learned that para-aminobenzoic acid will inhibit the growth of many of the rickettsiae and that it has a dramatically beneficial effect on the course of Rocky Mountain spotted fever in animals and man. Secondly, a virulent purified antigen is now available for complement fixation and agglutination tests and for the preparation of a potent vaccine. Finally, the insecticide DDT has been shown to be active against the various species of ticks which are responsible for the transmission of this disease to man and animals and has been of value in controlling these ticks.

For detailed discussions of the etiological, epidemiological and pathological aspects of Rocky Mountain spotted fever, readers are referred to the excellent reviews prepared recently for these clinics by Topping¹ and Baker.² The clinical aspects of the disease in children have been discussed by Martin³ and by Ong and Raffetto.⁴

TREATMENT

Para-aminobenzoic Acid.—Para-aminobenzoic acid is, at the present time, the drug of choice for the treatment of children suffering from Rocky Mountain spotted fever. Its action against the rickettsiae of louse-borne typhus fever was first reported in 1942 by Snyder and associates⁵ and independently in 1944 by Greiff and Moragues.⁶ Soon after these studies, experiments were carried out to determine its effectiveness against the rickettsiae of Rocky Mountain spotted fever. It was shown to inhibit the growth of these rickettsiae in the yolk sacs of fertile hens' eggs (Hamilton, Plotz and Smadel⁷) and to prolong life or prevent death in experimentally infected guinea pigs (Angstein and Bader⁸). Subsequently, several reports have appeared describing the use of this drug in the treatment of the disease in humans (Rose,⁹ Maroney,¹⁰ Flinn¹¹ and their respective associates, Hendricks and Peters¹² and Woodward¹³). Woodward¹³ treated thirteen children between the ages of 1½ and 10 years. All but one recovered and this

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one death occurred in a 2-year old child in whom treatment was not started until the nineteenth day of his disease Flinn¹¹ and his colleagues treated four children, 4 to 11 years of age, and all recovered Maroney and co-workers¹⁰ and Hendricks and Peters¹² have each treated one child with recovery

A comparison of the mortality rate in this group of nineteen children with the over-all rate for children under 15 years of age is not statistically valid. However, a comparison of the course of the disease in the group treated with para-aminobenzoic acid and in children not treated with this drug is both valid and significant. In all instances the children who have been treated with para-aminobenzoic acid and who have recovered have had shorter, milder courses. The number of complications has been smaller. The duration of fever and hospitalization has been about one week shorter. Within twenty-four hours of the administration of the drug a dramatic and remarkable improvement has been noted. The patients are more alert, more talkative, eat better, and begin to sit up and play with their toys. The rash disappears quickly, the temperature falls to normal within two to four days, and the patients can be discharged from the hospital shortly afterward.

Experimental studies indicate that para-aminobenzoic acid acts by inhibiting the further growth of rickettsiae. It does not affect the rickettsiae already in the body, nor does it repair the damage already done to the blood vessels. On the other hand, it does not interfere with the normal development of immunity. Guinea pigs infected experimentally with the rickettsiae of Rocky Mountain spotted fever and treated with para-aminobenzoic acid were later shown to be immune to challenge doses which were fatal to control groups of guinea pigs (Amigstein and Bader³). And in children treated with para-aminobenzoic acid there has been a normal development of antibodies as shown by the rise which takes place in the complement fixation titer.

Para-aminobenzoic acid should be given as soon as the diagnosis of Rocky Mountain spotted fever is suspected. It causes few, if any, dangerous reactions and can be tolerated in large doses. It is excreted rapidly by the kidneys and at the end of four hours blood levels have returned to concentrations which are not therapeutically effective. For this reason large doses must be given at frequent intervals during the day and night. It is recommended that whenever possible para-aminobenzoic acid be given by mouth or by gavage. An initial dose of 4 to 6 gm. should be followed by 2 to 3 gm. every two hours day and night until the temperature has been normal for two to three days. Sufficient drug should be given to maintain a blood concentration of between 30 and 50 mg. per 100 cc. Flinn and associates¹¹ suggest that satisfactory levels can be obtained with smaller doses by restricting the fluid intake. However, because of the great importance of main-

taining an adequate fluid intake in sick children, and particularly in children with Rocky Mountain spotted fever, adequate blood levels should be obtained by increasing the dose of the drug rather than by decreasing the fluid intake. Children tolerate para-aminobenzoic acid well and there appears to be no necessity for limiting the fluid intake. Blood levels of para-aminobenzoic acid can be determined by Eckert's¹¹ modification of Bratton and Marshall's¹⁵ technic for measuring the concentration of sulfanilamide in the blood.

Para-aminobenzoic acid can be given either dissolved in a chilled solution of 5 per cent sodium bicarbonate or as the acid or sodium salt in chilled orange juice or grape juice. Children prefer the drug when it is given in orange or grape juice. When the pure acid is given an equal amount of 5 per cent sodium bicarbonate should be given at the same time. If the sodium salt is given, no extra bicarbonate is required. The drug can be given by gavage to those children who are comatose, delirious or uncooperative. In older children a pressed tablet of the sodium salt is probably the best method of administering the drug. This tablet, because it is broken up and absorbed more slowly, gives rise to higher and more prolonged blood levels. Para-aminobenzoic acid may be given parenterally and this route may be necessary in those few children who vomit the drug when it is given by mouth. The sodium salt can be given intravenously but is excreted rapidly. For this reason it is perhaps better, as suggested by Woodward,¹⁶ to administer it in a continuous intramuscular drip. A 25 per cent solution of sodium para-aminobenzoate in a solution of isotonic sodium chloride is used. The pH of this solution is brought to 7.0 by the addition of small amounts of the pure acid and then it is sterilized by filtering through a Seitz filter.

Solutions of para-aminobenzoic acid should not be given subcutaneously to patients with Rocky Mountain spotted fever. Many of these patients have some degree of edema and under these conditions subcutaneous fluids will not be absorbed well.

Para-aminobenzoic acid has given rise to very few untoward side reactions in children. Woodward¹³ states that a few children have become delirious and irrational when the blood level exceeded 60 mg per 100 cc. These symptoms, however, quickly disappeared when the blood level was permitted to fall. Others have reported no toxic symptoms. Yeomans and his co-workers,¹⁷ who studied the effects of para-aminobenzoic acid in patients with louse-borne typhus fever, noted that in a few instances the white blood count fell below 5000 per cu mm and in one case to 1850. There was no change in the differential white count and the total count returned to normal with the cessation of treatment. They noted no deleterious action of the drug on the excretory functions of the kidney.

No attempt should be made to administer para-aminobenzoic acid by mouth to children who are so sick or so uncooperative that aspiration of the drug may result. This accident has been reported once in an adult male (Yeomans¹⁷). Death occurred and at autopsy a severe tracheitis was found. If the possibility of aspiration exists the drug should be given by gavage or parenterally.

Serotherapy.—Since 1940 an anti-Rocky Mountain spotted fever rabbit serum has been available for the treatment of patients with this disease. It is prepared by using either infected ticks or highly infected yolk sac material as the antigen. In 1943 Topping¹⁸ studied the effects of this serum in both animals and man. He showed that if adequate doses are administered on or before the third day of the rash a reduction in the severity and mortality of the disease can be expected. To the present time this serum has been given intramuscularly rather than intravenously. This has perhaps been an unnecessary precaution but was recommended in the belief that the use of intravenous fluids of any sort is contraindicated in Rocky Mountain spotted fever. This point will be discussed in greater detail below.

The recommended dosage of the serum is 1 cc per kilogram of body weight administered on or before the third day of the rash, according to the following schedule (Topping¹⁸). (1) A conjunctival test with normal rabbit serum is carried out, if negative, (2) 1 cc of the antiserum concentrate is administered intramuscularly, if there is no reaction after another period of ten minutes, (4) the remainder of the recommended dose up to 40 cc is given, (5) if more than 40 cc of antiserum is required, the remainder should be given twelve hours later. Those who have used antiserum recommend that it be repeated in full doses every two to three days. However, with the discovery of the success of para-aminobenzoic acid in the treatment of Rocky Mountain spotted fever the present indications for the use of antiserum are not entirely clear.

Biotherapy.—Penicillin has been used in the treatment of experimental infections in animals and has been shown to be of no particular harm or benefit (Fitzpatrick¹⁹). One instance of its use in the treatment of a 14 year old boy is reported but the results are difficult to evaluate (Edmunds²⁰). However, penicillin is of great value in the treatment of many of the complications of Rocky Mountain spotted fever and should be used in full dosage when these occur. There are no reports on the effect of streptomycin in this disease in either animals or man.

Sulfonamides.—Sulfonamide drugs should never be given to patients with suspected or proven Rocky Mountain spotted fever. Not only are these drugs of no benefit but they have been shown to increase the severity of the disease in man and the mortality rate in

animals (Martin,³ Burdick,²¹ Edmunds,²⁰ Fitzpatrick,¹⁹ Topping,²² and Steinhaus and Parker²³) In one instance their use may have contributed to the death of a child suffering from Rocky Mountain spotted fever (Burdick²¹) Many sulfonamide preparations, including pron-tosil, sulfapyridine, sulfathiazole, sulfaguanadine, sulfadiazine and sulfamerazine, have been tried in the treatment of experimental infections in animals and all have been found to affect the course of the disease adversely The use of these drugs in the treatment of Rocky Mountain spotted fever is contraindicated, save perhaps for the treatment of certain complications occurring during convalescence

Diet and Fluids.—During the last three years several careful clinical and metabolic studies have been carried out on patients suffering from both louse-borne typhus fever and Rocky Mountain spotted fever (Yeomans and associates,¹⁷ Woodward and Bland,²⁴ Harrell and co-workers^{25, 26, 28} and Dingle's group²⁷) The results of these studies, when interpreted in the light of the known pathological changes, have done much to elucidate the alterations which take place in the fluid, electrolyte and nitrogen balances and have helped to explain some of the clinical phenomena which occur during the course of these diseases

The *principal pathological changes in both louse-borne typhus fever and Rocky Mountain spotted fever* are found in the endothelial and smooth muscle cells of the smaller vessels of the skin and subcutaneous tissues The invasion of these cells by rickettsiae results in the formation of intravascular thrombi and necrosis of the blood vessels These, in turn, lead to extravasation of blood into the tissue spaces and account for the typical hemorrhagic appearance of the rash In addition to the formed elements of the blood which are lost into the tissue spaces, fluid, chlorides and plasma proteins are also lost There results a situation which is analogous to that which arises in persons who have been severely burned. The shift in chlorides and plasma proteins from the blood to the tissue spaces alters the osmotic pressure relationships and results in edema in these areas The level of plasma protein is further reduced by the failure of the liver in this disease to synthesize proteins adequately Furthermore, the loss of fluid and plasma proteins from the circulating blood gives rise to a reduced blood volume There follows a lowering of the blood pressure and glomerular filtration pressure, which in turn predisposes to circulatory collapse and prerenal azotemia. This tendency to develop azotemia is further promoted by the extensive destruction of body protein which takes place It does not appear that the development of azotemia is due to the effect of the disease on the kidney per se (Yeomans¹⁷) Woodward and Bland¹⁴ showed that the circulatory collapse depends on peripheral circulatory failure rather than on failure of the heart.

They found no evidence of cardiac enlargement by either physical examination or roentgen examination. Venous pressure determinations were always low. Electrocardiographic tracings were normal and there was no evidence of circulatory congestion of the lungs.

It has been generally felt for several years that the use of intravenous fluids was contraindicated in the treatment of Rocky Mountain spotted fever. This belief was held because it had been noted that animals treated with intravenous fluids died more quickly and patients similarly treated did less well than others not given intravenous fluids. The alterations in the fluids, electrolyte and nitrogen balances explain why solutions of glucose and saline, when given by vein, have a deleterious effect on the course of the disease. In an effort to correct the osmotic pressure relationships these fluids will be drawn into the tissue spaces and at the same time they will undoubtedly wash more protein out of the blood vessels into the tissue spaces. In this way a vicious cycle is established which only intensifies the changes which have been noted to take place. However, as will be shown later, if proper attention is paid to the type and amount of solution used, intravenous fluids can be given and should be given to most patients.

It has been mentioned that para-aminobenzoic acid merely inhibits the growth of rickettsiae. It does not affect any rickettsiae present in the body, nor does it repair damage already done to blood vessels. Therefore, *in addition to para-aminobenzoic acid these patients should be given proper supportive therapy* which will carry them along through the acute inflammatory phase of the disease and until the stage of healing sets in. Harrell^{25, 26, 28} and Dingle²⁷ and their associates, on the basis of their studies and with an appreciation of the changes which take place in Rocky Mountain spotted fever, have worked out such a treatment program and have used it successfully in the treatment of children. Essentially, this program is designed to reestablish and maintain normal physiological relationships between the fluid, electrolyte and protein fractions of the circulating blood and the tissue spaces. A diet low in fat and high in protein and carbohydrate is prescribed. Large supplements of vitamins are added. These are given by mouth or by gavage, depending on the condition of the patient. The diet is low in fat because of the known damage to the liver. It is high in protein to help replace body protein which has been destroyed or plasma protein which has been lost into the tissue spaces. This diet is supplemented by carrying amounts of blood plasma, albumin or whole blood given by vein.

The basic diet for those able to take food *by mouth* contains 2.5 to 3.0 gm of protein per kilogram of normal body weight per day. This diet, as recommended by Dingle²⁷ and her co-workers, is divided as follows: protein 70 gm, carbohydrate 145 gm and fat 57 gm. The

gavage formula for those unable to swallow or to take the basic diet is a concentrated feeding containing 0.9 Cal per cc. It is made up of skimmed milk 850 cc., powdered milk (casein) 100 gm, corn syrup 75 gm with large added supplements of vitamins A, B, C, D and K. This formula should be warmed before being given. It has a taste and consistency similar to that of malted milk and when flavored with chocolate syrup can be drunk from a cup. Of eight children treated by Harrell only one did not require a supplementary feeding by gavage at some time during the disease. These diets have resulted in no constipation or diarrhea.

In this manner as much as 115 gm of protein and 118 gm of carbohydrate were given to a 4 year old boy in twenty-four hours, and on this regimen, too, most patients maintained their weight or gained weight. This is to be compared with losses in weight amounting to as much as 7 kg in control groups. Patients given this high protein diet required less plasma and blood by vein to maintain nearly normal protein levels.

The administration of fluids *by vein* should be guided by frequent laboratory determinations and by a consideration of the physiological changes which have been shown to take place. Laboratory determinations should be made of the blood nonprotein nitrogen, serum chlorides, plasma proteins, the carbon dioxide combining power and the urinary output. In one instance 2800 cc of whole blood and plasma were administered in ten days to a 2 year old boy weighing 11.7 kg. In another instance 2500 cc of plasma were given to a 15 year old boy within thirty-six hours. It will often be necessary to give large amounts of plasma, whole blood or albumin in order to maintain an adequate circulation (Harrell and others²⁸).

A replacement program such as has been described will not succeed in every instance. In some instances it is probable that damage to blood vessels will be so great that irreversible changes analogous to those found in medical shock will take place. Proper diet and protein replacement therapy will not decrease the permeability of impaired capillaries but will help to maintain a normal blood volume until healing takes place.

Nursing Care.—Almost as important as specific chemotherapy with para-aminobenzoic acid and diet and fluid therapy is the general nursing care of the patient. These patients must be kept quiet. Careful attention must be paid to the skin to prevent the formation of decubital ulcers. Because of the danger of gangrene at pressure points, no restraints should be used.

Cardiac Stimulants.—Statements are found in the literature recommending the use of cardiac stimulants and peripheral vasoconstrictors for the treatment of the "cardiac failure" and circulatory collapse that

occur In view of Woodward and Bland's²⁴ studies, it is believed that such drugs are not only of no benefit but may be contraindicated They should not be used except in those patients who have preexisting heart disease

PREVENTION

Topping²⁹ has shown that in the Eastern part of the United States 46.8 per cent of the cases of Rocky Mountain spotted fever occur in children under the age of 15 years, while in the West only 14.4 per cent occur in this age group This difference may in part be explained by the habits of the two important tick vectors In the West the vector is the adult of the common wood tick, *Dermacentor andersoni* It is found principally on large mammals, such as the deer, elk and mountain goat Therefore, children are unlikely to become infested with this tick In the East the vector is the dog tick, *D. variabilis* It is found on dogs, cats, horses and cows, and because of this children are subject to infestation

Prevention of Infestation—The prevention of Rocky Mountain spotted fever in children should begin with an attempt to protect children from tick infestation Areas known to be infested with infected ticks should be avoided. It is not practical to dress children in summer with tick-proof clothing However, ticks do not attach themselves to the skin immediately but may crawl around for two to three hours before beginning to feed, and to cause infection it is believed that they must feed for several hours For this reason it is possible to take reasonable precautions by examining, carefully, twice a day, all children who are permitted to play in tick-infested areas All parts of the body must be examined, particular attention being paid to the axillae, pubic region, behind the ears, between the toes and to the scalp Parents should, if possible, keep the hair of a child's head short, for ticks on the scalp may be difficult to find

Removal of Ticks.—If a tick is found on the clothing or attached to the skin great care should be taken when removing it Individuals have become infected from handling ticks A forceps should be used and gloves should be worn *The removal of engorged ticks with the bare hands is a dangerous practice* The mouth parts of an engorged tick are usually embedded in the skin Several methods can be used to remove the tick without breaking the body and head from the mouth parts The latter, if not removed, are apt to cause a severe secondary infection Simple traction with the forceps will many times suffice to remove a tick This failing, a drop or two of kerosene or cigarette lighter fluid can be placed on the head Others bring the flame of a match or cigarette lighter near the tick Both of these methods will cause the tick to withdraw the mouth parts The tick will then either fall off or can be picked off easily Following removal, the tick should

be quickly burned. The point of tick attachment should be cleaned, an antiseptic applied, and a dry dressing put in place. These bites may at times become infected with enlargement of the regional lymph nodes.

Children frequently pick up ticks from their pet dogs or cats. These animals are often found to be heavily infested, and in a recent study (Shepard and Topping³⁰) half of thirty dogs examined were found to have clinical and/or serological evidence of infection with the virus of Rocky Mountain spotted fever. Furthermore, many of the dogs with positive findings came from families in which cases of Rocky Mountain spotted fever had occurred during the preceding weeks. The exact role that dogs play in the epidemiology of this disease is not clear, but it is apparent that they can serve as a source of ticks and that measures should be taken to keep them free of ticks and to prevent their bringing ticks into the household.

DDT is effective against dog ticks. It should not be used in solution or emulsion, for a 5 per cent solution of DDT in oil will be absorbed and is therefore dangerous to small animals, emulsions are irritating save when incorporated in a sponge bath. However, the 10 per cent DDT powder can be used and is effective. It has been recommended (Westerfield,³¹ Vet Med ³²) that one-fourth to one-half teaspoonful be dusted into the fur at the base of the neck and along the back of medium sized dogs. This dusting should be repeated at weekly intervals or oftener depending on the degree of tick infestation. In addition to treating dogs and cats, 10 per cent DDT powder should be dusted lightly into rugs, upholstered chairs or sofas and other places where these animals are accustomed to lie. If dogs and cats do become infested the same care should be used in removing the ticks from them that is used when removing ticks from children.

In exceptional circumstances consideration should be given to the treatment of tick-infested ground and vegetation. If playgrounds or picnic areas are found to be infested, the local public health authorities should be requested to treat these areas with DDT. Smith and Gouck³³ and Bishopp and associates³⁴ have shown that the population of the ticks *D. variabilis* and *Amblyomma americanum* in a given area can be reduced 90 to 99 per cent by the application of a total of 2 to 3 pounds of pure DDT per acre. This amount can be applied in either powder or solution form and areas so treated will remain practically free from ticks for a month or more. Glasgow and Collins^{35, 36} have used DDT incorporated in a thermol aerosol insecticide fog. Preliminary studies indicate that this method holds great promise for the treatment of local areas.

Immunization.—Two vaccines are available for immunization against Rocky Mountain spotted fever (1) a killed vaccine

from an emulsion of ground up infected wood ticks and, (2) a killed vaccine made from rickettsiae cultivated in the yolk sacs of fertile hens' eggs. Both of these preparations are of proven value and all children residing in or planning to visit areas known to be infested with infected ticks should be immunized. Immunization will not necessarily prevent the disease from developing but it does result in a marked attenuation of the symptoms, and controlled studies (Parker³⁷) indicate that the fatality rate is lower in immunized individuals than in those who have not been immunized prior to infection. Children may be given the same dose as is recommended for adults, namely, two injections of 2 cc each at an interval of five days. Following this initial course, a booster dose should be given at the beginning of each Rocky Mountain spotted fever season. If the egg vaccine is used, care should be taken not to administer it to children who give a history of sensitivity to eggs or egg products.

SUMMARY

1 Para-aminobenzoic acid is, at the present time, the drug of choice for the treatment of children suffering from Rocky Mountain spotted fever. It must be given in large doses at frequent intervals. It is well tolerated. Anti-Rocky Mountain spotted fever rabbit serum is of proven value and may be used in certain cases. Penicillin is of no value in the treatment of Rocky Mountain spotted fever, but should be used for the treatment of complications. Sulfonamide preparations should never be used for the treatment of suspected or proven cases of Rocky Mountain spotted fever. Diets high in protein and low in fat should be used. In many instances large amounts of plasma, whole blood, or albumin will be required by vein. Cardiac stimulants are contraindicated.

2 Measures should be taken to prevent children from becoming infested with ticks, and when infested great care should be taken when removing ticks. In tick-infested areas dogs and other household pets should be dusted with DDT throughout the tick season. In exceptional circumstances, consideration should be given to treating infested ground and vegetation with DDT. All children exposed to infestation with infected ticks should be immunized against Rocky Mountain spotted fever.

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HYPERINSULINISM AMONG MALINGERERS

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The diagnosis of hyperinsulinism caused by a tumor of the islands of Langerhans is usually not difficult. The story of hypoglycemic reactions in a patient who is not receiving insulin is suggestive. Such a patient has a story which follows a definite pattern. Symptoms are present only when he has not eaten or has exercised and he is promptly relieved by the administration or ingestion of glucose or sugar.

Corn and his associates¹ have reported a case in which hyperinsulinism was proved to be caused by the self-administration of insulin. He proved this by finding the patient's bottle of insulin and introducing some typhoid vaccine. When next she gave herself an injection she had both insulin and vaccine reactions.

I wish to present three other cases in which hyperinsulinism was self-induced

REPORT OF CASES

CASE I.—The patient was admitted to the Mayo Clinic on January 3, 1940, when she was 28 years of age. She had been well until 1935 when, following an appendectomy, she had gained in weight and by the following spring (1936) had presented the characteristic symptoms of diabetes mellitus. She was a rather unstable diabetic and in an effort to control her diabetes more carefully she had learned to determine the concentration of blood sugar. In January, 1937, she required 72 units of insulin daily. At about that time her requirement for insulin began to decrease and by April, 1937, she required none. She reported that in October of that year she had a fasting blood sugar reading of 60 mg per 100 cc of blood and that in August, 1938, she had her first severe reaction during which she estimated she was unconscious for six hours. Other severe reactions followed, but there were periods of several months during which she would have no symptoms. While the patient was undergoing a fast in a hospital in August, 1939, the level of blood sugar was found to be as low as 22 mg per 100 cc. The findings at surgical exploration the following month were

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COMPLETE UROLOGIC EXAMINATION IN INFANTS AND CHILDREN WITH URINARY INFECTION; INDICATIONS AND IMPORTANCE

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INFECTION of the urinary tract is one of the commonest diseases in infants and children and its high incidence is the more keenly appreciated when it is realized that most infections pass unrecognized. In many of this last group of cases, the condition is asymptomatic, casual urinalysis may suggest a normal urine. Here the infection is recognized only by culture or microscopic examination of the gram-stained sediment from centrifuged aseptically collected specimens. Yet with present day bacteriologic laboratory procedures, the development of a refined urologic armamentarium and increased diagnostic facilities such as excretory (intravenous) urography, there is no excuse for failure to recognize and identify the specific character of urinary infections as well as the gross morphologic changes they may engender.

Investigations in the young have revealed that with the exception of certain neoplasms of the lower urinary tract, adults and children are subject to the same urologic conditions. The diagnostic and therapeutic methods employed in each age group are identical. In the development of many of the more severe and/or persistent urinary infections in the young, anomalies are often associated etiologic factors because they commonly cause urinary obstruction. Thus a variable degree of urinary constipation exists which not only favors the development and perpetuation of urinary infection but nearly always must be eradicated before sterilization of the urine can be achieved. Moreover, these obstructions must always be removed if further urinary back-pressure damage of the proximal urinary tract, and especially the kidneys, is to be prevented. Yet conditions other than anomalies of the urinary tract are frequent associated or predisposing etiologic factors in urinary infections (Fig 96) and unless they are identified and corrected, cure of the disease as evidenced by urinary sterilization may not be achieved.

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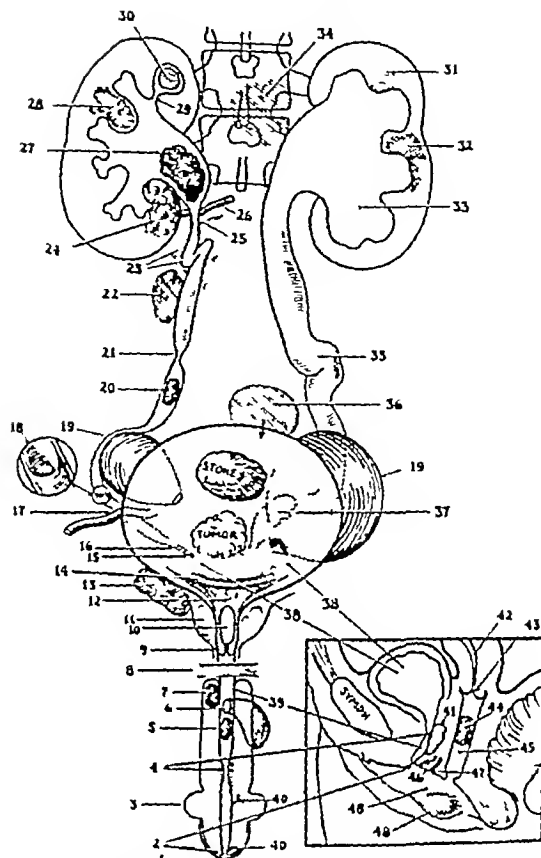


Fig 96—Direct and indirect causes of pyuria. These lesions, the clinical manifestations of which so commonly lead to the inadequate diagnosis pyelitis, either acute or chronic, can be identified only by a thorough urologic examination. 1, Stenosis of prepuce, 2, stenosis of urethral meatus, 3, paraphimosis, 4, urethral stricture, 5, urethral stone, 6, urethral diverticulum, 7, periurethritis, periurethral abscess, 8, cowperitis, chronic external sphincterospasm, 9, congenital valves of posterior urethra, 10, hypertrophy of verumontanum, verumontanitis, 11, prostatitis, prostatic abscess, 12, contracted bladder neck, median bar, 13, periprostatitis or pelvic suppuration, 14, mucosal fold at bladder outlet, trigonal curtain, 15, stricture of ureteral meatus, ureterocoele, 16, ureterovesical junction stricture, 17, vascular obstruction of lower ureter; 18, congenital ureteral valves, 19, ureteral obstruction by diverticulum compression, 19', diverticulum, 20, ureteral stone, 21, ureteral stricture, 22, periureteritis, periureteral phlegmon or abscess, 23, ureteral kink, periureteral fibrous bands, 24, renal tumor, 25, ureteropelvic junction stricture, 26, aberrant vessel obstruction of upper ureter, 27, pelvic stone, 28, renal tuberculosis, 29, stricture of calyceal outlet, 30, calyceal stone, 31, pyelonephritis, 32, pyonephrosis, 33, "pyelitis", infected hydronephrosis, 34, perirenal suppuration invading urinary tract, spinal disease (Pott's, etc.), 35, hydroureter; 36, pericystic abscess rupturing into bladder; 37, seminal vesiculitis, 38, neuromuscular vesical disease, 38', cystitis, 39, urethritis, 40, folliculitis (Morgagni), 41, periurethritis, periurethral abscess, 42, endometritis, 43, cervicitis, 44, foreign body in vagina, 45, vaginitis, 46, skenitis, 47, folliculitis of introitus, 48, Bartholinitis.

INDICATIONS FOR UROLOGIC EXAMINATION

Continuing studies of the urinary tract—and particularly in its relation to bodily development and welfare as a whole—have considerably broadened the indications for urologic examination in patients of all ages. In the young the following conditions definitely call for thorough investigation and it should be borne in mind that occasionally other indications may exist

- 1 Pyuria
 - (a) Acute persistent
 - (b) Chronic
- 2 Disturbances of urination—dysuria, frequency, urgency, etc
- 3 Hematuria (except acute nephritis)
- 4 Abdominal pain
- 5 Abdominal tumor
- 6 Anomaly of external genitalia
- 7 Urogenital injury
- 8 Hypertension
- 9 Renal insufficiency
- 10 Enuresis
- 11 Spinal cord injury and disease
- 12 Retarded growth

In the present discussion we are concerned with pyuria as indicative of urinary infection but appreciate that in some cases of urinary infection, disturbances of urination are the provocative symptoms or there may be abdominal pain, tumor, external genital malformation, injury and the other conditions above enumerated. In several patients who were referred because of so-called enuresis, the basic lesion was unrecognized urinary infection and from three of these children tuberculous kidneys were removed. Such observations are clinically monstrous but unfortunately do occur in the practice of medicine.

Examination of the Urine.—Urinalysis is the keystone of the urologic diagnostic arch and should properly be a part of every physical examination. Many of our most advanced cases of urinary infections have been unexpectedly detected by urinalysis accompanying a routine physical examination. When urinary infection is suspected, under investigation or therapy, only aseptically collected specimens merit the labor of meticulous examination and only the reports of such specimens should be seriously considered. This is especially true in females, irrespective of age. The casually voided specimen from young females is likely to be contaminated by vulvar debris and certainly the bacteriologic study of such a specimen is worthless. Even if it were of benefit, the trauma of scrubbing the vulva is infinitely greater than that of urethral catheterization gently performed with a small instrument and under visualization.

In males a satisfactory specimen can usually be obtained if, after retracting the prepuce and washing the glans and meatus with an

antiseptic solution such as oxycyanide or bichloride of mercury 1:500, a few cubic centimeters of urine are voided before some is passed into a sterile collecting receptacle. This is the only method by which extraneous bacterial and cellular contamination can be eliminated. If this method cannot be carried out, catheterize. Five to six pus cells per low power field of an uncentrifuged urine specimen is considered the top normal limit yet it is of little moment whether the pus cells are clumped. Great care should be exercised to identify as pus cells only those leukocytes showing the polymorphic or pawn-broker's nucleus. Too commonly epithelial and other cellular elements and even blood are erroneously interpreted as pus. If only freshly voided or freshly shaken uncentrifuged specimens are examined, the quantitative estimation of inflammatory elements in the urine offers a ready index to the progress of the disease and the efficacy of therapy.

In addition to the usual routine urinalysis, the aseptically collected specimen should be subjected to culture or to examination of the gram-stained sediment from freshly and aseptically collected urine which has been centrifuged at high speed (2500 revolutions per minute) for at least five minutes. This will reveal at once whether we are dealing with gram-positive streptococci or staphylococci for example, or gram-negative rods of the colon-typhoid and associated groups. There is some difference of opinion as to whether stain or culture is the more accurate but failure to identify organisms in the stained sediment specimen will usually be confirmed by a sterile culture. Yet it is notable that cultures and stained sediment specimens will often give false negative results when the specimen is taken during or just at the end of a course of chemotherapy. Here the stained sediment specimen findings are likely to be more accurate than the cultural. We should therefore wait at least three or four days after the cessation of all chemotherapy before taking the specimen for test-of-cure examination. Moreover, no patient should be discharged as cured of urinary infection until at least two negative cultures of aseptically collected specimens have been obtained. Less rigid criteria explain the common "recurrences" of apparently cured infection which, in truth, had merely been rendered dormant.

UROLOGIC EXAMINATION

Precystoscopic Data.—Before subjecting any patient to urologic instrumental investigation because of urinary infection, the invading bacteria should be precisely identified and an attempt made to sterilize the urine by medical treatment according to specific chemotherapeutic bacterial indications. For example, one does not employ penicillin for colon bacillus infection but sulfonamide or mandelic acid compounds or, specifically, streptomycin. If the infection remains acute despite

intensive medical therapy for three to five days, or chronic pyuria persists after two or three weeks of treatment, a complete urologic examination is indicated. Here excretory urography is the next step.

Excretory Urography.—By excretory or intravenous urographic study we may expect a satisfactory roentgenographic delineation of the upper urinary tract in at least 50 per cent of the children in whom it is employed. In general, the younger the patient the less likely will the excretory study be of diagnostic value. Yet in patients of all ages, it often gives invaluable precystoscopic information as when hydronephrosis, ureteral obstruction, calculi, diverticula and so forth are demonstrated.

Our present day chemotherapy of urinary infection will often be successful even in the presence of obstruction, calculi and other major urologic lesions. Therefore, when chronic urinary infection has been proved by two negative cultures to have been eradicated by chemotherapy and before the patient is discharged as cured, at least an excretory urographic study should be made to determine that the upper urinary tract is morphologically normal. The previous persistence of the infection strongly suggests the existence of asymptomatic urinary obstruction which, if permitted to remain, may be expected to continue to cause injury of the proximal urinary tract.

Study of the excretory urograms will often direct special attention to one kidney and/or ureter at the time of cystoscopy and retrograde pyelography.

Unfortunately many normal kidneys have been removed because of misinterpretation of the excretory urogram, the good kidney was removed while the diseased one was left. In such cases the fast draining normal kidney is thought functionally deficient while unrecognized ureteral obstruction on the opposite side caused sufficient renal pelvic retention of the excreted media to make this kidney appear to be the sound one. Therefore, surgical attack on the upper urinary tract and particularly nephrectomy should not be carried out on excretory urographic studies alone except in those rare instances in which ureteral catheterization cannot be performed as in tuberculous obliterative ureteritis, ureteral hypoplasia or because of insurmountable technical difficulty.

Having obtained this essential data, cystoscopy, ureteral catheterization with divided renal function tests, and bilateral retrograde pyelography are carried out and may be expected to reveal both the fundamental organic condition (stricture, stone and so forth) as well as the associated secondary uropathology. The wide variety of lesions which may cause or may be etiologically associated with acute or chronic urinary infection are indicated in Figure 96.

Instrumental Examination.—The indications for thorough urologic

examination have been outlined, lack of such an indication or inability of the physician properly to perform such an examination are the only contraindications. Instruments have been developed by the writer with which cystoscopic investigation can be carried out in the youngest patient of either sex. We have performed bilateral retrograde pyelography in several boys under four weeks of age.

Anesthesia—General anesthesia is required for cystoscopy in less than one fourth of all children. The pre-examination administration of relatively large doses of barbiturate compounds allays apprehension which is generally the chief obstacle to smooth instrumentation. I commonly employ seconal which is fast acting and of short duration. For example a grain and a half of seconal one hour before cystoscopy will usually cause a 4 year old child to sleep through the examination. When general anesthesia is required because of patient misconduct, unusual technical difficulty or pain, open drop ether or intravenous sodium pentothal are our choices.

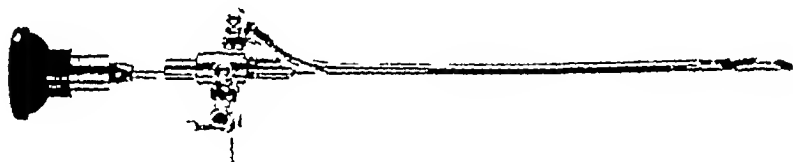


Fig 97—The smallest practical double catheterizing cystoscope (Campbell 13 F). It will carry two No 3 or "small" No 4 F catheters and permits bilateral catheterization and retrograde pyelography in all female and in most male infants.

Reactions to cystoscopic examinations are less frequent and severe than in adults and fear of febrile or other reaction should never be permitted to deny the sick child the advantage of such an examination when a bona fide indication exists.

URINARY INFECTION

Pyuria.—Nearly all urinary infections are accompanied by pus in the urine and until the nature of the infection is determined and the correct anatomic diagnosis is made, it seems best to identify the condition as pyuria. In the past and in some quarters today, the urinary infection is loosely designated as pyelitis but this term is clinically inadequate and almost always pathologically incorrect. Urinary infection limited to the lower urinary tract is common enough and, when the kidney is involved, the pelvic inflammatory lesion is generally

negligible. Pathologically the usual lesion is an interstitial suppurative nephritis. Moreover, it is important to recognize that most of the demonstrated pyuria originates in the suppurative lesion in the interstitial substance of the renal parenchyma. With this pathologic picture in mind one readily appreciates why severe and permanent renal damage so often results and why, in the presence of urinary obstruction, the renal infection becomes chronic and refractive to chemotherapy. Finally, renal sclerosis may even increase following bacteriologic cure of the infection and in some instances be clinically designated as Bright's disease.

The wide variety of renal infection processes which are loosely yet usually clinically designated under the blanket term pyelitis are as follows:

- 1 Bacteriuria—bacilluria
- 2 Pyelitis Anatomic (experimental), not clinical
- 3 Pyelonephritis
 - acute
 - chronic
- 4 Infected hydronephrosis
- 5 Pyonephrosis
- 6 Acute renal suppuration
 - (a) Diffuse suppurative nephritis
The pyemic kidney
 - (b) Focal suppurative nephritis
 - (c) Renal carbuncle
- 7 Renal infarction and thrombosis
- 8 Perinephritis and perinephritic abscess
- 9 Infection of ureter, bladder and lower urinary tract
- 10 Urinary tuberculosis

Of the foregoing, acute and chronic pyelonephritis and infected hydronephrosis are the most commonly encountered forms of urinary infection in the young.

Acute Urinary Infection.—Most acute urinary infections are clinically self-limited and disappear spontaneously irrespective of treatment. While it is probably true that in half to three fourths of these cases the urine ultimately becomes spontaneously sterile, in a surprising number culture of catheterized specimens taken two to four months following the acute attack shows persistence of the initial invading organism. For this reason the demonstration of a sterile urine must be the test of cure rather than an afebrile asymptomatic child.

When there is no apparent improvement during three to five days of intensive medical treatment, a complete urologic examination should promptly be carried out. As a rule the hyperacute infection process has been engrafted upon preexisting obstruction. Moreover, the histopathology explains why nephrectomy must be the ultimate

treatment in so many cases of "persistent acute pyelitis" which in fact may be severe acute infected hydronephrosis consequent to ureteropelvic junction blockage by stricture or aberrant vessel, acute suppurative pyelonephritis, diffuse suppurative focal nephritis, acute renal thrombosis and infarction, renal carbuncle or perinephric abscess

Chronic Pyuria.—When urinary infection persists longer than four weeks it is designated as chronic. The demonstration of persistent pyuria may reflect a previously unrecognized urinary infection or the asymptomatic persistence of acute infection thought cured. Fully 90 per cent of the major uropathies in children are due to urinary infection and/or obstruction and any condition which produces urinary constipation not only favors the development of infection but seriously interferes with therapy. The various potential causes of urinary infection are shown in Figure 96. It is notable that more than half of all urologic investigations in children will be made because of persistent urinary infection.

Among the commoner lower urinary tract lesions should be mentioned congenital stenosis of the external urethral meatus in each sex, and congenital stricture of the urethra. Both readily respond to periodic progressive dilation with sounds although meatotomy must often be employed in males. Congenital and neurospastic contracture of the vesical outlet, congenital urethral valves of the prostatic urethra and congenital hypertrophy of the verumontanum generally cause pronounced urinary obstruction with variable vesical residuum, dilated upper urinary tract and severe renal damage. As a result of these lower urinary tract obstructions, vesical calculi and diverticula are occasionally observed. Neuromuscular disease of the urinary channels is usually manifested by considerable dilation with variable urinary retention, the clinical picture is apt to be patchy. If the obstruction is unrelieved, the patient may be expected to die of renal failure. Infection may be anticipated in all cases of bladder neck obstruction and in most instances the investigation which discloses the congenital obstruction will have been carried out because of persistent pyuria. Transurethral removal of the obstructing tissue through the miniature resectoscope readily and almost bloodlessly eradicates the blockage.

Congenital urogenital malformation, particularly of the upper urinary tract, occurs more often than in any other system in the body. The incidence of anomalous ureterorenal development in children with chronic pyuria is approximately twenty times that observed in nonpyuric individuals. Congenital ureteral stricture is the commonest of these obstructions and perhaps the most frequently recognized. Yet ectopic ureteral orifice, ureterocele, vascular obstruction of the ureter and other ureteral obstructive lesions interfere with drainage and cause hydronephrosis which may be expected to become infected. In

massive hydronephrosis the obstruction is usually at the pelvic outlet and the higher the obstruction is in the ureter, the more severe will the hydronephrosis be

Renal tuberculosis is the underlying disease in approximately one in sixty cases of persistent pyuria in the young and is likely to be overlooked except when secondary vesical involvement causes distressing symptoms. Here complete urologic examination may be expected to reveal the nature and severity of the renal lesion which, if unilateral, calls for nephrectomy

SUMMARY

Attention has been directed to the high incidence of urinary infections in the young and the potential gravity of these bacterial invasions. At the present time more urologic examinations are carried out in infants and children for pyuria than for any other reason. Yet the scope of the urologic problem in the young is almost as broad as in adults. The indications for urologic examination have been given and the various requisites of adequate urologic examination have been discussed. Careful urinalysis of properly collected specimens should be a part of every complete physical examination and is mandatory in every sick child. Only by giving these young patients the advantages of thorough urologic examination, can we hope to determine the nature and severity of the existing disease as well as the most rational therapy.

reported as negative. During October and November she had occasional reactions and she had had none during December.

She was a patient at the Mayo Clinic from January 3 to April 10, 1940, from October 21 to December 21, 1940, from October 25, 1941, to January 16, 1942, from March 18 to July 4, 1942, from March 26 to September 22, 1943, and from December 16, 1944, to February 17, 1945. It is impossible to include all of our studies. In summary it may be said that the patient's symptoms and the laboratory findings were consistently those of severe organic hyperinsulinism. Between 1940 and 1942 several operations were performed in an effort to find an adenoma of the islet cells of the pancreas. Dr. Waltman Walters operated first on January 19, 1940. No tumor was found and a ligation of the pancreas was done. On November 29, 1940, he explored the pancreas again. The ligation had caused the disappearance of the body and tail of the pancreas. No tumor was felt in the head of the pancreas. A biopsy of the liver showed it to be normal. Because of the patient's continued hypoglycemia another exploratory operation was performed on November 25, 1941. Marked regeneration of the pancreas had taken place and a subtotal pancreatectomy was carried out. Another partial pancreatectomy was performed on March 24, 1942, and again on May 22, 1942. Following the latter operation frank diabetes appeared, but the patient continued to have severe episodes of hypoglycemia interspersed with episodes of diabetic acidosis. In 1944, the patient was carefully studied in Boston and another exploratory operation was performed there, primarily because of adhesions.

Thus this patient underwent a total of seven exploratory operations but an islet cell adenoma was not found and the hyperinsulinism was not improved. Presumably as a consequence of surgical removal of almost all pancreatic tissue, she had become diabetic. The persistence of hyperinsulinism in the presence of diabetes was, to say the least, most unusual. Nevertheless, the deception remained quite complete. The patient was again hospitalized here and Dr. Keating finally became suspicious and had her removed from her room. A careful search revealed a supply of insulin and the bottles, after being marked, were replaced. When the patient was next unconscious the marked bottles told the story.

When confronted with this evidence the patient admitted that she had been giving herself unneeded insulin for several years, but she steadfastly refused to tell us the exact dates and insisted that early in her illness she had had genuine hyperinsulinism. With repeated reactions marked mental deterioration had occurred and I, therefore, do not believe her story. Life had treated her cruelly and my opinion is that she seized on these self-induced reactions as means for personal dramatization. Before her final dismissal she acknowledged that she had attempted suicide once with seconal and several times with in-

SOMATOPSYCHIC ASPECTS OF BEHAVIOR DISORDERS OF CHILDREN

LOUIS A. LURIE, M.D.*

For the past three decades a great deal of effort has been spent in spreading the tenets of mental hygiene, both to the medical profession and to the laity. The role of mental hygiene in industry, in education, in social service, in the prevention of crime and delinquency, was widely publicized and focused attention on mental functioning. The late war with its emphasis on the great incidence of neuroses and psychoneuroses in our population has focused even greater attention on the psychobiological aspects of man's reaction to his social milieu. However, because of the increasing acceptance of Freudian psychology and doctrines, the study of human behavior has tended to become more and more psychodynamically oriented. Since, to many, psychoanalysis is the essence of psychodynamic science, the entire approach is therefore psychoanalytical.

THEORIES OF HUMAN BEHAVIOR

At this point it may be well to call attention to the fact that human behavior has been a fascinating subject of study for a great many years and in the course of these years various schools of thought have flourished.

Possibly the first school of thought attempting to elucidate the riddle of human behavior was the so-called *organicist*. This school of thought held that mind or consciousness (and hence behavior) was merely the product of the functioning of the nervous system. As expressed by the physiologist Vogt, "the brain secreted consciousness in the same manner that the liver, for example, secreted bile." Mental functioning was merely an epiphenomenon resulting from neural activity. Evidence of this was of course not difficult to find, e.g., the commonly observed changes in personality, and clouding of consciousness to even complete disappearance of all mental activity as a result of pathological changes in the central nervous system due to tumor, inflammation, trauma and chemicals. This point of view was highlighted by Lombroso with his thesis that criminals were born and not made.

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The organicist was soon challenged by the *environmentalist* with his social approach to the study of human behavior. According to the latter, it was "nurture" and not "nature" that was responsible for human maladjustment whether in the form of delinquency, criminality or other type of antisocial behavior. Heredity versus environment became a prolific subject for discussion and argumentation. Ask the average person today what in his opinion is the most common cause of juvenile delinquency as well as of adult criminality, and he will at once answer "vicious environmental influences" under which are included poverty, slums and bad associates. A visit to any detention home or penal institution would seem to corroborate such an opinion. The work of Shaw¹ and his colleagues emphasize this. They showed that in Chicago there are certain crime areas—areas that seem to breed crime no matter what type of individual lives there. These areas were first inhabited by Poles, who later were followed by Italians. The latter in turn have been supplanted by Negroes. Each racial group as it replaced the other adopted its patterns of antisocial behavior with the result that delinquency and criminality continue to flourish in these areas.

It is interesting to note that each of these schools developed offshoots that are of more than historical interest. For example, the environmentalist approach to the study of human behavior led the psychologist, Watson, to formulate his theory of behaviorism. According to this theory human behavior is entirely environmentally conditioned. Furthermore, on the basis of Pavlov's work on the conditioned reflex, Watson denied even the existence of consciousness. All human behavior was due to environmentally conditioned reflexes. To quote Watson: "Give me a child from the moment he is born and permit me to control his environment and I will produce a saint or sinner as I choose."

Similarly the followers of the organicist school concentrated on the localization of functions in the brain. Attempts were even made to locate the seat of consciousness. Today lobotomy and lobectomy are recognized procedures in the treatment of various mental disorders.

With the advent of Freudianism both the organicist and environmentalist were supplanted and emphasis was placed on the *psychodynamic* interpretation of human behavior. Organic as well as sociological factors were brushed aside in favor of such psychological factors as frustration, repression, Oedipus complex, and the like.

The psychodynamic orientation in the study of personality and human behavior has now gone further and has spread to involve other fields of medicine. Under the appealing title of psychosomatic medicine, no disease entity is now sacrosanct from the implication that it may be due in great part, if not entirely, to psychological factors. Ac-

cording to this view, peptic ulcer, essential hypertension, asthma, chronic sinus infection, urticaria, coronary thrombosis and many other diseases are psychologically conditioned. In other words, psychological factors can produce alterations in cellular function and structure which changes may even be irreversible. As expressed by Rado,² "Social life, the psychological impact of one individual upon the other, produces emotional stresses and strains that can interfere with healthy function in any part of the organism. Therefore, in time, every department of medicine will have to be behavior-conscious or according to the current slogan—psychosomatic."

With the present trend toward psychosomatic interpretation in medicine in general and in the interpretation of human behavior in particular, there is great likelihood that the role of *somatic factors* in producing personality disturbances and abnormal human behavior will be neglected. This would be unfortunate. It should be remembered that one cannot separate function from structure. Genetically, function follows structure and changes with it. The development of the psyche or mind has been coincident and coextensive with the increase in the structural complexity of the central nervous system. To quote Rado³ again: "As an integrated whole, the human organism is almost completely controlled by the central nervous system, preeminently the cerebral cortex. The cortex in action, called psyche, or mind, dominates behavior." Hence anything that affects the structural integrity of the cortex must necessarily disturb the normal functioning of the psyche or mind and hence alter behavior.

An automobile may be driven over an embankment because of feelings of guilt which the driver harbors with the resultant need for punishment. Such unconscious motivations very often explain human behavior. However, one must not overlook the fact that this same automobile accident may have been brought about as a result of the driver suffering a cerebral hemorrhage or an anginal attack, or an epileptic seizure (somatic factors), or because of a broken tie rod or a tire defect (environmental factors).

In other words, in order to understand human behavior in all its manifestations, one must not only recognize the psychodynamic factors that may be present but also the somatic and sociological factors. In the last analysis, behavior merely represents the end results of the interaction between the individual as a psychophysical organism and his environment. Therefore to properly study and evaluate human behavior, we must have knowledge of the total situation. Such an approach envisions man as an organism whose behavior is conditioned by the integrity of his psychophysical make-up as well as by the nature of the environmental forces surrounding him. If this point of view is kept in mind, the organic or somatic factors involved in

the production of personality distortions and abnormal human behavior will not be overlooked

BEHAVIOR DISORDERS AND PERSONALITY CHANGES OF CENTRAL NERVOUS SYSTEM ORIGIN

Psychoanalysts are constantly reminding us of the importance of infancy and childhood from the standpoint of the development of the personality. The claim is made that the personality structure becomes fixed at a very early age—as early as five years according to some psychoanalysts and not until nine years according to others.

If this is true and bearing in mind the relationship of function to structure, the importance of the integrity of the brain during early infancy and childhood becomes highly important in this connection. Anything, such as infection, trauma or inflammation, that interferes with the normal development of the brain structure will be apt to interfere with the development of a normal personality structure.

Hence, when examining a child who presents a behavior difficulty or personality deviation it is important to record any occurrence that could possibly have deleteriously affected the child's nervous system. The physical condition of the mother during gestation as well as all the circumstances surrounding the birth of the child must be noted. Furthermore it is not sufficient merely to record that the child has had the "ordinary diseases of childhood." The age at which the diseases occurred as well as their severity and possible complications must be ascertained.

Pertussis Encephalopathy.—Any virus or bacterial disease may secondarily affect the central nervous system. For example, many studies have been made of the cerebral changes that may occur in whooping cough. Autopsies performed on infants dying from pertussis and its complications have revealed definite changes in the cerebral structure in the form of ischemic cellular degeneration, multiple hemorrhages, and lymphocytic plugs in veins and capillaries. Such changes are adequately described by the term "pertussis encephalopathy." The pathologic changes have been divided into three principal groups, namely, (1) hemorrhagic, (2) degenerative and (3) inflammatory. Various forms of mental abnormalities associated with these neuropathologic changes have been reported. That such results are not infrequent has been shown by Lurie and Levy.³ In an analysis of an unselected group of 500 problem children, it was found that 58 or 11.6 per cent had had whooping cough before the age of two years. Thirty-four or 58.6 per cent of this number later in life showed behavioral, intellectual and personality changes that appeared to be attributable to the neuropathologic sequelae of the whooping cough.

Postencephalitic Type of Behavior.—A great deal has also been

written about the relation of encephalitis to personality disturbances and behavior difficulties in children and adolescents. A fairly characteristic type of behavior, commonly termed postencephalitic type of behavior, has been recognized. The dominant personality traits of children showing this type of conduct are impulsiveness, lack of inhibition, extreme distractibility and unpredictability of behavior. One moment they may be loving and kind and the next moment they may be hurtful and hateful. Their attention span is short and lack of a goal idea is evident. Night terrors, habit tics, and respiratory difficulties are frequent complicating symptoms. Their conduct is at times so bizarre that very often they are erroneously diagnosed as schizophrenics. Failure to respond to either social or medical therapy is also characteristic of this group.

This type of disturbance is well illustrated by the following brief case report.

C. M., Jr., aged 6, was referred for examination because of peculiar behavior. A diagnosis of schizophrenia had been made. The parents related that the boy had spoken normally until the age of 3 years. Since then he has not spoken except for uttering an occasional word or two which were usually irrelevant. He is extremely hyperactive and destructive. His actions appear both unpredictable and uncontrollable. At times he is loving and at other times very hurtful without any apparent reason for the change in mood. He exhibits certain peculiar mannerisms, such as licking his fingers, grimacing, and placing his hands over his ears and muttering to himself. He eats ravenously, pushing the food into his mouth with his hand.

According to the medical history, birth was normal. He teathed, walked and talked at the normal time. At the age of 3 years he was able to recite the entire alphabet. When 2 years old he suffered a severe grippal attack. He ran a temperature for some time. In fact, the condition did not clear up entirely until his tonsils were removed six months later. At that time the father noticed a change in the child. He began to show peculiar mannerisms of the type mentioned above. In addition when asked a question he would merely repeat the question, no matter how often it was asked. Gradually he stopped talking altogether. Physically the child has been in good health, having had no illness since the tonsillectomy.

During the examination, the boy appeared entirely oblivious to his surroundings. He was extremely restless, moved from one place to another without any apparent goal, made facial grimaces, muttered to himself, and did not respond to either commands or entreaties. The neurologic examination revealed positive Chaddock and Babinski signs on the left.

In this case the medical history is revealing as it shows a definite break in the normal mental development of the child, following an attack of an acute infectious disease. The psychiatric sequelae in the form which is now recognized as postencephalitic type of behavior, could be ascribed to an encephalitis which occurred as a complication of the acute influenzal infection. More and more the role of the infectious and contagious diseases in infancy and early childhood in producing intellectual retardation, deviations in personality structure and behavior disorders is being recognized. Many obscure cases of be-

havior disorders become understandable only if evaluated in the light of a history of complications following an attack of one of the so-called "ordinary diseases of childhood"

The incidence of encephalitis in children presenting behavior disorders is by no means insignificant. Of the first 2500 problem children admitted for study to the Child Guidance Home, Greenebaum⁴ and his collaborators found the incidence to be 2 per cent.* The incidence is probably even greater since the disease, as a complication of acute infectious and contagious diseases of children, is frequently overlooked. One of the reasons for this may be that the neurological examination is often entirely negative. Another reason, and probably a more potent one, is that, in the great majority of cases, there is no history of an attack of encephalitis. It is only when the medical history of the child, as well as his behavioral reactions, is carefully scrutinized and evaluated from the standpoint of a possible encephalitic episode complicating an acute infectious or contagious disease occurring in the first decade of life, that the condition becomes apparent. We are in agreement with Bender⁵ that "The diagnostic criteria for encephalopathic behavior disorders are now considerable. Even without the history of a specific etiological factor or evidence of the specific (neuro) pathology, the diagnostic methods which may be applied to fields of behavior are sufficient to establish a diagnosis."

Furthermore, the longer a case is followed the more characteristic the clinical picture becomes. Often where only a suspicion of the condition was originally noted, reexamination years later easily establishes the correctness of the tentative diagnosis. As time goes on the pattern of behavior and characteristic personality structure becomes more clear-cut and pathognomonic. If these facts are borne in mind, many more cases of intractable behavior disorders and irreversible personality changes will be found to fall into this category.

Encephalitis illustrates better than any other disease that changes in the structure of the brain may lead to changes in function. Since the encephalitic process may attack any part of the brain, the disorganization of function will correspond to the level or levels of the brain stem involved. Hence, vegetative, motor or intellectual dysfunction either alone or in combination may be present.

There is considerable diversity of opinion regarding the genesis of the psychopathological train of events. According to some investigators, the encephalitis merely brings out character defects and abnormal personality traits that were already present but had been dormant. According to others, encephalitis does not necessarily accentuate the premorbid personality. "The tragic feature of encephalitis is personality change, not personality exaggeration."⁶ This belief seems

* In a later investigation Greenebaum and Lurie found the incidence to be over 3 per cent.

to be borne out by the fact that the psychopathological after-effects of encephalitis are much more pronounced in patients affected early in life. Furthermore, from a study made at the Child Guidance Home, it would appear that the younger the patient affected by the disease, the greater the likelihood of psychiatric sequelae.

It is important that this condition be recognized if for no other reason than that the blame for failure to secure good results will be placed where it belongs. The failure of social therapy and psychotherapy in these cases cannot be attributed to faulty social or psychiatric techniques. Rather, such failure indicates that the problem of the child presenting postencephalitic behavior disorders or personality changes is not solely one of psychodynamics. The psychopathological symptoms in these cases are primarily due to the neuropathological changes and it is our present medical inability to correct the latter which accounts for the failure of treatment. These cases illustrate very pointedly the relation of function to structure in human behavior.

BEHAVIOR DISORDERS AND PERSONALITY CHANGES RESULTING FROM ENDOCRINE DISORDERS

Pathological changes in the soma that may directly or indirectly be responsible for abnormal behavior are not necessarily limited to involvement of the central nervous system.

Disturbances in the normal functioning of the endocrine glands are potent causes of personality changes and behavior disorders. To quote Hoskins: "In so far as one honestly repudiates the mind-body dysfunction, he must concede an important role to the hormones as determinants of personality."

This is readily understandable when we realize the important role played by the glands of internal secretion in the growth and development of the individual. It is safe to say that there is hardly a single bodily function that is not directly or indirectly influenced by them. They are concerned with differentiation of tissue, with nutrition and growth, with sexual activity and with mental development. In brief, they are intimately bound up with all development, physical as well as mental. Not only is our stature and shape and sexual functioning largely determined by the various glandular secretions, but our intellectual capacity and personality make-up as well.

Direct and Indirect Effects of Endocrine Dysfunction on Personality and Behavior; Adiposogenital Dystrophy.—When we attempt to correlate specific forms of endocrine disorders with definite types of personality disturbances, it is essential to clarify the situation by first recognizing that the effect of endocrine dysfunction on the personality and behavior are of two kinds. The effects may be classified as (a) direct and (b) indirect.

The syndrome of adiposogenital dystrophy is characterized by a triad of symptoms, namely, dwarfism, genital infantilism and adiposity of the monomammmary-girdle type of distribution. Such children are small, fat and fair, and have a distinctive personality make-up. They are as a rule cheerful, happy and apparently contented, which fits in with the universal belief that fat boys and girls as well as adults are jolly and good-natured and well behaved. Their mental reactions, however, are slow and hence they may be very irritating and annoying to others who feel that their slowness of response is indicative either of lack of interest or carelessness. In fact, such children often give the impression of mental retardation, whereas in the majority of cases, the opposite is true.

From the behavioristic standpoint, children presenting this syndrome can be classified as belonging to the submissive-compliant type. Their lack of aggressiveness is outstanding. They are shy, gentle, easy-going, timid and artistic—traits that are usually considered effeminate and which are in harmony with their physical appearance. This is especially noticeable in the case of boys who because of the broad pelvis, rounded curves, fair moist skin and rosy cheeks, high-pitched voice, and absence of hair on face and lips have a distinctly feminine appearance. As aptly stated by David Levy,⁸ "their social adaptation to life is in the main one of easy compliance and submissiveness." They avoid strenuous physical exercise and the stress and strain of competitive work and sports. They prefer the arts to the sciences.

Their patterns of behavior and personality traits are due to the hormonal deficiency and can be looked upon as the direct effects of the pituitary endocrinopathy upon the personality.

In addition to the direct effects of hormone dysfunction on mood, thought and behavior, there are often indirect effects. This applies to the reaction of the individual to the knowledge that he is suffering from a disturbed bodily function. This often produces emotional conflicts of great severity, with resultant marked personality changes.

The girl who because of an adrenocortical involvement has a marked growth of hair on her face and chest may react to that knowledge by withdrawing completely from all social contacts, or she may seek refuge in a life of fantasy and unreality. On the other hand, her escape may take the form of suicide.

Similarly the boy whose genitalia have remained infantile because of gonadal insufficiency may develop a shut-in type of personality or he may resort to bribery, trying with treats of candy, movies or the like to get into the good graces of the gang and thereby stop the constant allusions to his infirmity. Many a youngster has resorted to stealing in order to carry out such a plan.

On the other hand, this boy, instead of withdrawing into himself or

attempting to curry favor through bribery, may become antisocial. He may develop feelings of hostility against society because of the hurt his ego has suffered and he will replace the passive submissive personality which the hypogonadal condition has foisted upon him with an aggressive sadistic attitude that will make him attempt to get even with the world. This may be the underlying motivation for a life of crime.

It is this failure to distinguish between the direct and indirect effects of the endocrine dysfunction upon the mental and emotional make-up of the individual that has led to considerable confusion in thought regarding the specificity of the correlations between endocrinopathic states and personality disturbances. In pituitary disorders as well as in other endocrine dysfunctions, there are certain broad personality changes that occur with such regularity that they must perforce be looked upon as causally related. The clinical picture presented in such cases may vary, however, because of the varying degree of intensity of the indirect effects of the endocrine dysfunction which may be superimposed upon the direct effects. The indirect effects may be looked upon as the subjective effect upon the individual of the knowledge of his incapacity or infirmity. Obviously, this will vary with each individual and will depend largely on his native or constitutional endowment, on his past experiences, and on his social milieu. The indirect effects lead to a feeling of inferiority in the true Adlerian meaning of the term. To what extent the organ inferiority will develop and what mental mechanisms may be produced as a result, can be predicted only when the totality of the situation is known.

Homosexuality.—Nowhere is the relationship between changes in hormonal level and modifications in the behavior patterns of the individual seen more strikingly than in the study of homosexuality or sex inversion. To the psychoanalyst, homosexuality represents an arrest in the normal psychosexual development of the individual as a result of various abnormal psychological processes. However, even Freud was forced to the conclusion that this explanation was not sufficient. To quote from his "Three Contributions to the Theory of Sex": "The unsatisfactory conclusions which have resulted from this investigation of the disturbance of the sexual life are due to the fact that we as yet know too little concerning the biological processes in which the nature of sexuality consists, to form from our isolated examination a satisfactory theory for the explanation of either the normal or the pathological."

That the underlying biological processes are endocrinological or hormonal is assumed by many. Much experimental evidence has accumulated tending to show that sexual behavior is due primarily to specific qualities of the male and female sex hormones. Thus, Henry'

in a study of 228 homosexuals showed a high degree of correlation between the homosexuality and the inverse constitutional make-up. Women suffering from arrhenoblastoma show a marked inversion of the sexual urge or drive. Similarly, Neustedt and Myerson¹⁰ in a quantitative sex hormone study of twenty-nine overt homosexuals found a marked disturbance in the normal androgen-estrogen ratio. The deviation from the norm took one of two directions: (1) a decrease in the androgens combined with a normal amount or excess of estrogens, or (2) a normal amount of androgens combined with an excess of estrogens.

However, it must be borne in mind that, notwithstanding the fact that a fairly large proportion of sexual inverts have the secondary physical characteristics of the opposite sex, sexual inversion can exist without any demonstrable anomalies of the constitutional or morphological make-up.

This apparently paradoxical situation can be explained if we revise our classification of homosexuality.

Homosexuals have usually been divided into two broad groups, overt and latent. A better classification is that of *innate* and *acquired*. These terms are self-explanatory. Such a classification will avoid some of the criticisms directed at the purely psychoanalytical concept of homosexuality and at the same time explain the paradoxical situation mentioned above. The psychopathology of acquired homosexuality may be correctly explained on a purely psychodynamic basis. The condition of the innate homosexual on the other hand can best be explained on the basis of the presence of a somatic factor in the form of an endocrine dysfunction. The results of such a somatopsychic approach was reported by the author¹¹ in a recent publication. Because of its instructive value, one of the cases reported in this study is cited in detail.

R. O., a white boy of 13, was referred for study because of his marked effeminacy. Because of his feminine mannerisms, actions and high-pitched voice, boys called him "sissy." The general physical examination was negative. The endocrine examination revealed the following pertinent facts: The boy had the female type of skeletal development, the pelvis was broad and he was knock-kneed. His waist was extremely small, and his fingers were long and delicate. His skin was fair and smooth. His face was distinctly feminine in appearance, the skin being fair and highly colored. There was no hirsutism either on the face or in the axillae. His breasts were exceptionally large. The penis and testes were normal in size but there was a female hairline. Androgen determination showed a secretion of only 7 IU in twenty-four hours.

The boy realized that he was not as masculine as most boys and had tried to compensate for this by forcing himself to become interested in athletic sports. In this he had not been especially successful. He was more successful in amateur dramatics. He liked to study and was on the honor roll in his class. When younger he played only with girls. He helped his mother with the household tasks and particularly enjoyed helping with the cooking and baking.

sulin Shortly after her dismissal, she died at home reputedly from diabetic coma. This report from a relative was not corroborated by a physician's statement.

CASE II—A young woman, 32 years of age, was admitted to the Mayo Clinic on December 21, 1945. In June, 1942, diabetes mellitus had developed. From then until June, 1945, she had had several episodes of acidosis, some trouble with insulin reactions, a carbuncle, and so forth. In June, 1945, her reactions had become more severe and more frequent even though for six weeks prior to her admission she stated she had taken no insulin. Yet in spite of the fact that she had not been taking insulin, she had continued to have reactions of such severity as to produce unconsciousness and generalized convulsions. She had been referred with a diagnosis of spontaneous hypoglycemia, caused either by an adenoma of the islands of Langerhans or by hepatic failure.

Following admission the patient had severe hypoglycemic reactions,

the lowest reading of blood sugar was 22 mg per 100 cc. She and her sister were told that a study of the skin temperature was important. The patient was removed to the laboratory where thermocouples were taped to her fingers and toes and where she was kept for twenty-four hours. During this time the levels of blood sugar rose as they would in any other diabetic patient, in this case the level rose to 267 mg per 100 cc. The patient was a graduate nurse and she and her sister were much on the defensive. Since it was desirable to have conclusive evidence, permission to administer radioactive phosphorus was asked for and granted. The patient was given an injection of sterile water while she was receiving the so-called studies of skin temperature. Dr Keating then went to her room and after a diligent search found bottles of insulin. He injected the radioactive phosphorus into these bottles. The following day when the patient was unconscious in another reaction her urine was tested with the aid of a Geiger counter and found to be strongly radioactive.

The following evening we informed the patient and her sister that the episodes of hyperinsulinism were known to have been self-induced. Even when confronted with the empty insulin bottles found in the snow beneath the patient's window they refused to acknowledge the deceit. With permission the patient was given amylal intravenously and interviewed again. Under narco-sis she not only confessed that the attacks were self-induced, but also revealed the deeply rooted psychic disturbances which had led to her behavior.

CASE III—This patient had been admitted to the Mayo Clinic for the first time on August 30, 1943, when she was 16 years of age. Diabetes had developed five years before and the patient had been

At the age of 10 the boy began to have nightly emissions. These were accompanied by vivid dreams. In these dreams a naked man who was being whipped unmercifully by another man would appear. The boy looked forward to these dreams, as they gave him a great deal of emotional satisfaction. He did not understand the nature of the emotion that was thus aroused. The men in the dreams were always big, muscular, broad-shouldered individuals with slender waists. For the past year he had begun to masturbate during these dreams. Recently the dreams had varied somewhat from the original ones in that one of the naked men tortured the other by either burning his penis or by sticking pins into it. He admitted that several times he had seen naked boys and men of this particular build and that they had aroused a strong sexual urge in him. Girls never aroused him in that manner. He had often seen his mother in the nude but she had never aroused any sexual desire in him.

Although he had been greatly aroused on various occasions by the sight of nude boys and men, he had always been able to restrain himself from embracing them. Such sights, however, would produce strong erections and a great desire to masturbate. The boy had practically no knowledge of the anatomy of the female sexual organs nor of the physiology of sex in general. He did not know how the sexual act was performed.

Treatment with testosterone propionate was instituted. Injections of 25 mg were given three times a week. As improvement was noted, the injections were gradually reduced to twice a week, and finally discontinued entirely. The first improvement noted was a change in the pitch of the boy's voice, which became much lower. Hair began to grow on his face and gradually his whole physical contour changed. He lost his feminine curves and his breasts became smaller. The boys stopped calling him "sissy" and began to cultivate his friendship. Interestingly, he told that, coincident with these structural and personality changes, the content of his nightly dreams had changed. He began having dreams with heterosexual content. A woman entered into the dream at first she merely undressed the man and admired his slim waist and muscular build. In succeeding dreams, the woman also undressed. The man would touch her breasts and then they would both go to sleep. These dreams did not excite him and never led to orgasms.

After six months of treatment, the patient began to feel a thrill when standing next to a girl. He noticed that he desired the company of girls more and more. Boys did not thrill him any more in the manner they had formerly. When finally discharged, he was in all respects a normally aggressive male. At no time during the course of treatment was any attempt made to treat the boy psychoanalytically. The psychodynamics of the case were not discussed. Only a simple explanation of the rationale of the endocrine therapy was given.

CONCLUSION

Today the major trend in psychiatry is to explain human behavior in terms of Freudian psychology. The tendency to minimize and even to ignore the role of somatic factors in the causation of abnormal behavior has proceeded to the point where even psychiatric social workers feel competent to diagnose and treat behavior disorders of children and adults without the aid of the physician or psychiatrist. A thorough medical evaluation of the patient is not deemed essential. This attitude on the part of psychiatric social workers has been strengthened by the statements of some psychoanalysts that the usual set-up of workers at a child guidance clinic, consisting of psychiatrist,

psychologist and psychiatric social worker, can be dispensed with. The claim is made that any person trained in psychoanalytic concepts, and hence psychodynamically oriented, is qualified to diagnose and to treat personality disturbances and behavior disorders.

Such a trend must not be condoned. As physicians, we must recognize that we cannot separate function from structure. Genetically, function follows structure. The development of the psyche or mind has been coincident and coextensive with the increase in the structural complexity of the cerebral hemispheres. Hence, anything that affects the structural integrity of the cortex must necessarily disturb the normal functioning of the psyche or mind and hence alter behavior.

In this paper the role of various somatic factors in producing intellectual retardation, personality distortions and behavior disorders in children has been discussed and the importance of a thorough physical evaluation of the child has been emphasized.

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THE EARLY RECOGNITION OF CHILDHOOD SCHIZOPHRENIA

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As a rule, psychotic, neurotic and behavior disorders of childhood are first recognized and referred for treatment, though not necessarily diagnosed, by pediatricians. This is especially true of the preschool age group. While schizophrenia is not a common disease of childhood, its severity and the inevitability of its outcome, after it is firmly established, give considerable importance to its early recognition. Indeed, in recent years, an increasing number of children have been brought to the attention of the psychiatrist with the presenting complaint raising the question of differential diagnosis, and schizophrenia being one of the diagnostic possibilities.

Apart from the rare instances of an accurate diagnosis at the earliest possible stage, two tendencies are noted, which point to the need of a closer analysis of diagnostic criteria: one, is to overlook apparently minor deviations which are potentially malignant, the other, to make an early diagnosis on isolated symptoms which, while they may bring additional evidence to the over-all picture of the syndrome, are not particularly characteristic of the disease.

This paper is not a formal presentation of criteria for differential diagnosis, but rather represents an attempt to give helpful hints on the early indications of schizophrenic illness in childhood.

There is actually no satisfactory formulation of childhood schizophrenia as a disease entity, the symptomatology, on the whole, is described by comparison with the adult syndrome, or in terms of its later developments, during adolescence and adulthood. Nevertheless, it is now recognized by psychiatrists and pediatricians alike.

From all reports dealing with course and prognosis, it is known that chances for total recovery are almost nil, and for relative recovery only slight, when treatment is started after the syndrome is fully developed. Whether the prognosis would be good if the illness were recognized in its earliest stage is not known, the literature offering no enlightenment on this point for an obvious reason: namely, that even cases with acute onset were either presented for psychiatric treatment after some delay, or else were not identified until the acute episode

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had subsided, and profound personality changes had already taken place. However, from general clinical experience, and from reports on more recent methods used in the treatment of schizophrenia, it can be assumed that the earlier the disease is identified, the earlier can treatment be initiated, and results be obtained

ACUTE ONSET

Although the demarcation between acute and insidious onsets, with their manifold variations, is not always sharp, this demarcation is retained for purposes of convenience. Acute onset will first be considered. When the symptoms are well characterized, there should be little or no difficulty in making an early diagnosis, owing to the intensity and severity of these symptoms. In a previously well- or relatively well-adjusted child, with no indication of organic illness, there suddenly appear acute symptoms in the nature of motor excitement, restlessness, sleeplessness—or else, stupor, posturing, muscular rigidity and catatonic attitudes, both pictures can alternate. There is evidence of auditory and visual hallucinations, delusions, and usually manifestations of regression in sphincter control as well. The child is confused, shrieks or mutters words or sounds which appear incoherent and irrelevant to the current situation. He may also become totally mute, or revert to more primitive forms of speech expression. The total picture is one of acute anxiety, which sedatives and ordinary means of reassurance fail to allay. The child is out of contact, and does not respond to the spoken word and entreaties of even the persons closest to him. He may or may not have an associated hyperthermy, but even this does not necessarily point to an organic etiology.

Such episodes are generally easily recognized, and distinguished from confusional episodes or deliria which are associated with acute fevers in childhood. The absence of organic illness or signs of toxic or infectious disease rules out delirium. Acute encephalitis, associated with infectious illness, is sometimes brought up as a matter of differential diagnosis, if the symptoms of the infectious illness are obscure or so benign as to have escaped detection. However, in the encephalitic syndrome, the motor restlessness and sleeplessness are more prominent than the delusional and hallucinatory content, whereas, the reverse is true in schizophrenic illness. Neurological findings also help to differentiate the two syndromes. Furthermore, in going carefully into the earlier adjustment of the child, it is usually found that there were deviations in the emotional relations of the child to his environment in the case of acute schizophrenic illness. They may have been slight enough for the mother to have, at first, presented the child's adjustment as normal, but on closer scrutiny, it is obvious that deviations which will be described at length under the heading of "Insidious Onset," were present, although to a minor degree.

INSIDIOUS ONSET

It is in this category of cases that the diagnosis is most difficult, and generally made late in the development of the schizophrenic process. The illness may represent a slow, progressive development of deviations which were at the outset barely perceptible, or it may be ushered in by an acute exacerbation of mild deviations which were slowly developing over a period of years. In going over the early histories of such children, it can be seen that while their early psychomotor development was normal (for instance, they walked and talked at the normal age), their emotional and intellectual developments showed peculiarities, the significance of which has not been emphasized enough.

Dissociative Phenomena.—In a previous publication,⁴ I called attention to the early dissociative phenomena which are generally found in these children. The evidence of such dissociations is indeed noted as early as the second or third year. It appears in the form of detachment—not being a part of the group—which precedes the blunting and flatness of affect seen later in full-fledged cases. Very early, there is a lack of emotional relationship to people, the extreme of which is seen in Kanner's subjects with infantile autism who seem never to have developed a relation to people as people. Some schizophrenic children seem to look upon people as if they were inanimate objects. The withdrawal is not only a question of degree, but must be differentiated from ordinary day-dreaming—a certain amount of which is normal—to extents varying with social milieu, types of families, and individual make-ups. The withdrawal of the schizophrenic child is of a different order, and pathological. Associated with it there is an inability to differentiate between fantasy and reality, which is not observed in the normal child after the 3 year level, even when he indulges in a good deal of day-dreaming or fantasy acting.

The inability of the schizophrenic child to tie up emotionally with people in his environment can be considered a pathognomonic sign. Frequently, these children make statements which are very revealing, in that they exquisitely express the affective dissociation which exists long before the more dramatic symptoms have appeared. For instance, a 7 year old boy refers to his grandmother as "*an old girl called 'grandma.'*" A 12 year old girl makes repeated references to a man whom she calls by his first name, and who is obviously her father. When asked who this man is, she answers, "*He is my ancestor.*" On one occasion when she was away from home with her mother and she was asked if she missed anyone, she mentioned her dog but not her father who was also left behind. A very significant statement by a 1 year old girl, referring to her father, has been quoted in a previous publication.⁵ This child referred to her father as "*the man who sleeps here and has bacon and eggs in the morning that man.*" The same 4

year old girl when asked what she did at school, answered "Just hang your coat and sit on a chair" Numerous similar examples could be quoted from the records These expressions are illuminating, for they give the measure of a fundamental lack of emotional relationship with human beings, and in particular, the closest of all to a child—his parents It should be emphasized at this point that the schizophrenic child, when making the statements quoted above, is never facetious, as might be the case with a normal child if he ventured to make similar statements I wish strongly to emphasize these early dissociative phenomena, for in making a diagnosis of childhood schizophrenia, one must look for them It could safely be said that if they are lacking, the diagnosis cannot be made, for schizophrenia, whether of adult or child, is fundamentally a disturbance in affective contact While there are many definitions and interpretations of the basic concepts of schizophrenia as a disease entity, all authors are agreed at least on this point

Excessive Dependence on Mother.—There are other significant deviations in social relationships which warrant special consideration, and again the deviations, as described here, can be considered pathognomonic Notwithstanding the inability to tie up affectively in the family environment as pointed out, there is an excessive dependence on the mother or mother substitute, which is of a different nature than the dependence observed in neurotic or immature children This excessive dependence is not on the basis of emotional immaturity alone, as would be the case with these two categories Generally, the parents report the excessive dependence, and they do so with statements which are very characteristic The mother of a 4 year old girl remarked that the child "sees the world through me" The mother of a 4 year old boy complained that she could not be away from him even when he was in a play group, since he depended on her to initiate games, invite playmates, or fight his battles Although this 4 year old boy demanded the continuous presence of his mother, he also at times would say to his mother, "I can't use you now," as if his mother were to him an inanimate object which he could use or leave at will The words alone hardly convey the pathological nature of these statements, but the lack of emotional tone or the emotional inadequacy which is associated with them, once observed, are readily recognized for their contrast with normal expression

Bizarre Behavior.—Under the general heading of bizarre behavior, a variety of peculiar motor and behavioristic patterns are noted In this connection, again it is important to indicate that these motor and behavioristic patterns are bizarre—not so much because of their unusual structure, but primarily because the affect is inappropriate, and fictitiousness is lacking For instance, a normal child might, in fun put a wastebasket on his head, but he, as well as the observer, is

fully aware that this activity is carried out in fun, whereas, the 9 year old schizophrenic boy, John N, doing the same thing, walks about solemnly, with no expressed or hidden intention of fun. It is the lack of facetiousness, rather than the activity, that stamps the behavior as bizarre. Long before definitely autistic activities appear, there is observed in these children a tendency toward *nonfunctional play* which, to the thoughtful observer, is very striking. This again must be distinguished from the repetitive and purposeless activities of the feeble-minded who, for instance, may swing or rotate endlessly a toy not designed for this purpose.

There is often a characteristic rigidity in motor attitudes or, on the other hand, a variety of compulsive motor activities, the meaning of which may in the course of treatment be understood, but which on casual observation appear purposeless. In the latter category belong *rituals* and *compulsions* which differ from the passing rituals of young normal children, or more lasting rituals of neurotic children. The difference is more than a question of degree, since, in contrast to these children, the ritualistic patterns in the schizophrenic child seem dissociated from his total behavior. There is lacking the fluidity in verbal and motor behavior, which is so characteristic of the young normal child. These schizophrenic children often seem to be bound by a maze of rituals, which even the severe neurotics do not exhibit. Another point worthy of note is a *lack of conformism*, which is also so characteristic of the young normal child. With all of the individuality of the young child's behavior, it is readily recognized that children in a group spontaneously conform to certain patterns of behavior which the schizophrenic child ignores. The sum total of these deviations is an expression of the developing *away* from the normal frame of child behavior.

Temper Tantrums.—Temper tantrums have been stressed by the majority of authors as characteristic of the prepsychotic personality in schizophrenic children. It is true that they are almost always found in their early history and, as such, are a good index of their inability to take frustrations, but even when severe and numerous, they cannot be considered pathognomonic signs.

Speech and Language Deviations.—The speech development of these children is also of great interest. The failure to distinguish between first and third person singular is noted even in children as old as 10 or 12 years. The normal child does not refer to himself in the third person after approximately 3 years of age (and sometimes earlier). The persistence of this immature form in the schizophrenic child is one more indication of his pathological relation to the outside world, in that the I—not I distinction is not established. It is true that a child may be encouraged by his parents to use infantile forms of speech beyond the normal range, but in this case the infantilization

would be in keeping with other signs of immaturity, and not associated with the peculiarities described here

Very early, schizophrenic children show a tendency to dissociate sign from function in their use of language. They have an exaggerated, often obsessive interest in word forms—detached from the emotional and intellectual content which these forms normally carry. They are prone to play with words which are either too difficult or abstract for children of their age, or words which are not relevant to the interests of young normal children. This peculiarity must be differentiated from the normal, playful use of words as mere phonetics which is commonly found in children of the preschool age, and also, from the tendency toward repetitive speech of the retarded child who repeats words, because he has few to use, or because he is unable—through intellectual limitations—to grasp their meaning.

Schizophrenic children frequently coin words, the meaning of which is peculiar to themselves, although not necessarily totally unintelligible when the background of the neologism formation is known. Their need spontaneously to communicate with the outside world by means of accepted conventional signs is limited, and under such conditions, language structures are likely to develop without regard to semantic rules and usage. An error which is frequently observed is the diagnosis of schizophrenia in young children with a normal motor development, but with some retardation or anomaly in the speech development, the assumption being that the retardation or anomaly is an index of abnormal emotional development. However, intellectual retardation may be an end result of dysgenesis or agenesis which affects mainly the speech area. If disturbances of contact are not present, the diagnosis of schizophrenia on speech anomalies alone is not warranted.

Additional observations on the speech function bear on the speech peculiarities as they involve voice, pitch, rhythm and modulation. In the writer's experience, they are never lacking, and are probably related to the inadequacy of the emotional tone of speech content.

Contrary to findings on mentally retarded children, schizophrenic children give the impression of being intelligent, and when they can be tested, this impression is substantiated.

Age Level and the Behavior Pattern.—While the observations reported above do not apply to specific age levels—there is, nevertheless, a tendency for the symptoms to present differentiated patterns according to age levels. For instance, during the 2 to 5 year old level, disturbances in contact tend to be manifested in speech deviations, lack of social interest, bizarre behavior, nonfunctional play, and regressions in training. Delusional and hallucinatory expressions are seldom observed before age 5. Delusions of being an animal, for instance, occur in the younger age group, roughly between 4 and 6 years, while hypo-

chondriacal delusions do not appear before approximately 8 years. From 10 years on, the psychopathological picture tends more to resemble adult expression. At all levels, severe anxiety is present when acute symptoms develop.

Schizophrenic and Schizoid Behavior Compared.—A final point of interest bears on the differentiation between schizophrenic illness and behavior in the schizoid personality. In the schizoid child, malignant characteristics such as affective dissociations and delusional and hallucinatory experiences are lacking. Although the child is withdrawn and his social adjustment is poor, he does not set himself apart from others by exhibiting autistic manifestations and dissociative phenomena.

SUMMARY

While schizophrenia is not a common disease of childhood, its early recognition is important because of its severity and the inevitability of its outcome after it is firmly established. In this presentation, an effort is made to indicate early manifestations of the illness in childhood.

For purposes of convenience, a differentiation is made between acute and insidious onsets. Acute symptoms are readily recognized, and seldom confused with delirium or confusional episodes associated with acute fevers of childhood. It is in the cases with insidious onset that the diagnosis is most difficult.

Significant deviations from the normal are described, such as the early emotional detachment and lack of social relationship to people. This inability of the schizophrenic child to tie up emotionally with people in his close environment can be considered a pathognomonic sign. Notwithstanding this characteristic there is noted an excessive dependence on the mother or mother substitute, a dependence which is not on the basis of emotional immaturity alone as would be the case with neurotic or immature children.

Bizarre behavior is observed early, and includes a variety of peculiar motor and behavioristic patterns. Preceding the appearance of bizarre behavior, there is noted very early a tendency toward nonfunctional play. Temper tantrums, while frequently reported, cannot be considered pathognomonic.

The speech development is of significance, in that the I—not I distinction is established considerably later than is the case with the normal child. There is an exaggerated interest in word forms, detached from the emotional and intellectual content which these forms normally carry, and anomalies of voice, pitch, rhythm and modulation are noted.

While there is no absolute relation between symptoms and age levels, there is a tendency for certain symptoms to be more prominent

at different ages, with those of the preadolescent age range being most similar to adult pathology

Finally, a differentiation is established between schizophrenic illness and behavior in the schizoid personality

DISCUSSION

HOWARD W POTTER, M D *

Clinicians whose experience has provided an opportunity to study children with schizophrenic reactions will be quite in agreement with Dr Despert's description of the symptoms and course of this malignant emotional illness as it appears in even young children

Perhaps it will be helpful to the pediatrician if we explain, as a working hypothesis, that, in childhood schizophrenia, we are dealing with children who, constitutionally, have an inherent special disability to deal with their inner emotional tensions (anxiety) which are set up by environmental stress and personal relationships. Since, in such instances, the child is bound to feel helpless, a psychological "blotting out" of his environment serves to reduce his anxiety, thus relieving him of his feelings of helplessness and, in addition, he either regresses to earlier infantile modes of adaptation and behavior or remains fixed, in his emotional development, at these earlier levels of adaptation

Perhaps if the child psychiatrist could work with these cases at the initial stages of their schizophrenic illness, a more favorable outcome could be secured

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referred for regulation of this disease. There had been no complications and the disease had been satisfactorily controlled with 14 units of protamine zinc insulin and 40 units of regular insulin administered as a mixture once daily before breakfast

The patient was admitted for the second time on February 19, 1945. She had enjoyed good health and had not changed the amount of insulin until the summer of 1944, when she began to decrease the amount. By December of 1944 she was not requiring any insulin and yet continued to have severe reactions. She was referred to the clinic with the diagnosis of hyperinsulinism.

Following her second admission the patient had periods of hypoglycemia (lowest blood sugar reading was 38 mg per 100 cc) and periods of hyperglycemia (highest blood sugar reading was 258 mg). On February 22, with her mother present, her belongings were searched and her insulin was found. The bottles were marked and left. The next day she had another reaction and after administering glucose which resulted in the usual prompt recovery, I asked her when she had last taken insulin. She replied, "In December." I then opened her suitcase and her mother and I confirmed the fact that a large amount of insulin had been withdrawn since the bottles were marked. Even when confronted with this evidence the patient steadfastly refused to acknowledge that she had injected insulin into herself, unless she had done it unconsciously. Even under narcosis she would not change her story. However, she did stop her malingering and was dismissed with instruction to take a mixture of 12 units of protamine zinc insulin and 32 units of regular insulin once daily before breakfast.

COMMENT

The term "hyperinsulinism" should be reserved for those patients whose hypoglycemia is caused either by the injection of too much insulin or by a tumor of the island cells of the pancreas. Hypoglycemia also may be caused by severe hepatic insufficiency, or in association with Addison's disease or with severe pituitary insufficiency. Mild hypoglycemia with changes in the sugar tolerance curves is found in many nervous individuals in whom it can be considered a part of the clinical picture rather than a cause of their trouble.

Three cases have been presented to illustrate that hyperinsulinism may be produced as a result of malingering. All three were cases of diabetes. The first patient conditioned my colleagues and me for the diagnosis of the next two.

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FEEDING DIFFICULTIES IN EARLY CHILDHOOD

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ANOREXIA, although less common than a few years ago, continues to be one of the most frequent complaints for which children are brought to the pediatrician. Associated with the complaint of lack of appetite are other feeding difficulties, such as refusal to chew, refusal to take solid food, dawdling and vomiting. Usually the feeding difficulty is not an isolated complaint but is associated with other problems such as sucking habits, sleep disturbances, difficulties in bowel and bladder training, and with personality disturbances such as excessive shyness or aggression, negativism, insecurity or anxiety. When there are associated difficulties it is most likely that the anorexia is psychogenic and not due to organic disease. It is this group that will be discussed.

ETIOLOGY

The causes of feeding problems are many. One must make sure that the complaint is valid, that the child lacks appetite and not that he refuses what the parent wishes him to eat.

Rigid Schedule.—A rigid schedule is one of the most usual causes. The parent has fixed ideas as to what is good for the child and as to the quantity of food he should take. If he does not accept what is given and all that is given he is apt to be considered a feeding problem. He may eat with pleasure food that he likes, among the favorites being bread and butter, meat and fruit, but refuse vegetables and cereals which the parent feels are good for him.

Often parents complain of anorexia in children who are gaining well or are actually obese. Sometimes the complaint is that the child is never hungry, and never asks for food. This is a normal condition, after the first birthday and until school age it is unusual for a child to be hungry or to show much interest in his food.

Most feeding problems begin in the second year. At this time there is developing in the child his first attempts at independence. He is not only beginning to explore his environment but is making his first efforts to control it. If the parent exerts too much pressure as to just what and how much should be eaten the child is apt to rebel, and a

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feeding difficulty begins. There should be some leeway in amount and types of food.

During the first year of life the child triples his weight, gaining about 15 pounds. In the second year he increases his weight by only one fourth, a gain of 5 or 6 pounds. Parents and sometimes physicians do not appreciate that this means an actual lessening in the amount of food the child needs. Instead of decreasing the total amount of food after the first birthday, it is often increased. The child cannot eat it, the parents insist, and further antagonism toward food develops.

Stress on gain in weight and misunderstanding of the meaning of "normal" may cause the parent to be worried about anorexia when the child is actually doing very well.

Unappetizing Food.—A less frequent cause of refusal to eat in young infants is the unpalatability of the food. Because it is easier, some mothers continue to give canned baby foods for an unusually long time. Others continue this use because they actually believe that these foods have qualities particularly beneficial to the child. These foods are mushy, unseasoned and certainly not attractive in appearance. Peas, beans and spinach all look alike and none appeal very much to the child with a flagging appetite.

Delayed Training.—Delayed training is frequently the cause of feeding difficulties. There is an optimal time at which the child may be taught each new act and a time at which he may be expected to assume responsibility. There is a regular sequence of emerging potentialities and the ability to perform one act helps in acquiring the ability for the next. Thus, holding the bottle leads to holding the cup, the appearance of teeth and ability to chew allow the child to masticate chopped food and to bite cookies and zwiebach, manipulating the spoon precedes the use of the fork. If the child is not allowed to learn each act at the appropriate time he is not prepared to undertake the next one. At the proper time it is fun to feed oneself and there is a gratifying sense of accomplishment but two years later if the ability is not already established feeding oneself becomes a boring duty and one to be avoided if possible.

Overprotecting Attitude of Parents.—These difficulties become exaggerated under certain circumstances, especially where there is an overprotecting attitude toward the child. This produces an immature and infantile reaction in the child and is good ground for feeding problems. Among the most common reactions are insistence upon being fed, refusal to chew, refusal of solid food. These are frequently accompanied by other immature reactions such as refusal to take responsibility for dressing and undressing, delay in becoming self-reliant, temper tantrums and demands for attention.

An overprotecting attitude is most commonly shown toward a wanted child. His parents fear he will not eat enough if he feeds him-

self, so they feed him too long. His whims are catered to so that he will eat more. Too much attention is paid to height and weight tables and rate of gain. Vitamins, calories and balance of diet become too important and the child is watched too closely. Little account is taken of his likes and dislikes and coaxing and bribing are practiced to make him eat more. Soon, sensing that the feeding situation is a means of *gaining attention from his parents*, he insists upon puréed foods and upon being fed. When he feels that the attention is not adequate or not quickly enough manifested, vomiting occurs and calls for immediate action from the parents.

The Rejected Child.—Overprotection is commonly associated with overaffection toward the child but may occur in instances of rejection by the parents. Then the child is overprotected not because of love and anxiety but because of a sense of guilt in the parent arising from his lack of real affection for the child. He tries to compensate in material ways. The resulting feeding problems are similar to those accompanying affectionate overprotection but with the added demand for greater attention from an unwanted child.

More common in the rejected child is the revenge motive. In this instance the child is aware of the parental attitude, resents it and seeks revenge. He senses that his refusal to eat will upset the parent. Overauthority occurs frequently among rejecting parents. The child is forced to eat, and being afraid not to do so, he dawdles over his food or sometimes he eats it and vomits.

Summary of the Etiological Factors of Anorexia and Feeding Difficulties.—1 The most common factor is the lack of understanding of physiological anorexia of the second year. The child needs less food.

2 Rigid schedules, insistence on certain foods and upon certain quantities of food lead to a refusal to eat these foods.

3 Unpalatability, monotony, lack of spices and gravies and unattractiveness in service certainly do not stimulate the child's appetite.

4 Poor training is a potent cause of a child's refusal to feed himself.

5 Poor timing increases the child's dependence on his parents and insistence upon being fed.

6 Lack of understanding of the child's emerging self-dependence keeps the child infantile.

7 Emotional maladjustments between parent and child cause problems. (a) overprotection with either overaffection or rejection, (b) revenge as the result of rejection by the parents, (c) revolt against overauthority.

PREVENTION

Far easier than treatment of already existing feeding problems is prevention. In this field we know fairly well what to do and what to avoid.

The infant should be permitted to develop at his own speed. When he is ready to learn he should be helped to learn. Thus when he can sit up alone and hold his own bottle he should be taught to use the cup and, soon thereafter, the bottle should be discarded.

As soon as his appetite decreases toward the end of the first year or early in the second the amount of food offered should be lessened. Small helpings with an understanding that there is more in the kitchen is a good way to get him to ask for more rather than to refuse what he has on his plate.

Attractive service, tempting foods, variety and good preparation are as valuable in stimulating the appetite of the small child as of the adult. Eating should be made a pleasure not a duty.

At this age no single food is essential to the well-being of the baby. This is a hard lesson but an important one for the mother to learn. There is always a substitute. Also there are very few foods which are not well digested, so the child's diet may be interesting and include what he likes. Most children like meat and fruit, bread and butter and milk, a perfectly adequate diet. They dislike cereal, cooked vegetables and soups. Often they will eat raw vegetables and refuse cooked ones, if there is any difference the raw ones are more beneficial to the child. No single food should be insisted upon.

With his developing independence the child must be allowed some choice of behavior and of food. Too much authority at this time keeps him infantile if he is submissive, or if he is aggressive results in screaming, poor behavior and temper tantrums, excellent ground for the development of feeding difficulties.

Most important of course is a satisfactory home environment full of affection, encouragement and appreciation of the child's developing self-dependence. In such an environment where the child is secure in the love of his family and free to grow at his own speed no difficulties will occur.

TREATMENT

Treatment is much more difficult than prevention. Most important is the adjustment of the home environment so that the feeding problem is no longer the first concern. When the parents can be persuaded not to worry over whether the child eats or not the most important point has been achieved.

The parental attitude should be modified so the child feels he is loved and so that he need not strive hour after hour to assure himself of the attention of his parents.

He must be permitted to develop at his own speed. He must be helped in acquiring new habits and must be allowed to assume as much self-dependence as is compatible with his age. Holding his own cup and pouring from a pitcher will make eating more interesting. It is not important if he spills his milk or drops some food from his fork.

The child's skill will increase and presently feeding himself will become a habit. Along with self-feeding must go other manifestations of growing up, such as dressing and washing oneself.

Small helpings and attractive service will stimulate the child's appetite. At first very small quantities of food, which the child is known to like, should be given. Gradually these can be increased and other foods added but it is best to keep the amount put on the child's plate below the amount he eats willingly. If he refuses some certain food there should be no comment—not even if he refuses an entire meal. The child should never be told he can't have his dessert unless he eats his vegetables, pudding or stewed fruit is just as important as meat and vegetables.

Of course bribing and threatening should be stopped. Distracting the child with stories and games is no solution, for eventually nothing the parent conceives will be of sufficient interest to distract the child. It is better to stimulate the child's appetite with tempting and interesting food, then he will eat because eating is a pleasure.

To expect a small child to be hungry is a fallacy. After the first year and until near school age children are rarely hungry or ask for food. It is unwise also to ask the child what he wants. He has little appetite and he really does not want anything. Also the parent is apt to tell the child "You asked for it, you must eat it" when he was forced to make a choice.

Authority should not be exerted by the parent to make the child eat. The parent must appreciate the fact that satisfaction of his own ego is not the important point. Because he says so is not sufficient cause for the child to eat. And, more especially, because he says "eat this" is not adequate reason for the child to eat it. Perhaps he would prefer a substitute.

At this age children are imitative, and eating with other children helps eliminate feeding difficulties. Sometimes having the child eat with the family will help but unfortunately too often the child becomes the center of the stage and feeding becomes too important. In extreme cases it is necessary to have the mother out of the room during mealtime. The feeding situation is so charged with emotional tension that the child cannot relax sufficiently to eat his meal.

There should be no discussion of food. The father should not be informed whether or not the child ate his dinner, nor should the child be asked if he liked what he had. It is best to let eating become a routine. Gradually it will become pleasurable and usually by 5 or 6 years the child looks forward to mealtime.

Let us emphasize once more that there is no single food essential to the child's diet and further the amount for each child varies with his size, metabolism and health. If the child is well and can gain adequately on a minimum amount of food, that is sufficient. The fat

child is not known to be the healthiest child. Most children will eat adequately if the parent will assume a reasonable attitude toward the child and his food.

The feeding problem is rarely the only one. When it is associated with other difficulties the parental situation should be investigated. Is there overanxiety and overprotection? Is the child being watched all the time? Are the parents overaffectionate or do they reject the child? Is there too much authority and do the parents insist that the child eat what they want and the amount they want? Is there a nagging and overcritical attitude in the home? If any unfavorable situation is present it should be corrected. Only in an environment of affectionate encouragement can the child develop his full potentialities and grow up unhampered by behavior difficulties.

Summary —1 Assuring the parents that there is no need for anxiety will relieve the tension in the home.

2 Adjustment of parent-child relationship is of prime importance. Only in an environment of affectionate encouragement can the child develop his full potentialities.

3 Giving the child adequate affection and attention will lessen his need to use the eating situation as a weapon to gain attention.

4. Less rigid schedules with consideration of the child's likes and dislikes will help.

5 Attractive service and varied and palatable food will stimulate the child's appetite.

6 Small helpings are more pleasing than large ones.

7 Bribing, threatening and distracting the child only increase in his mind the importance of eating and never help the situation.

8 Eating with other children or with the family may eliminate some of the attention given to the eating situation.

9 Proper training in the use of eating utensils and in self-feeding, self-dressing and so forth gives the child a sense of security and helps him to grow up normally.

10 Some understanding of the child's potentialities and of his need to develop in his own way will be of aid. He must explore his environment, attempt to control it, battle for his independence if he is to develop into a normal self-reliant school child.

ILLUSTRATIVE CASE

E. S., a boy aged 2½ years, was referred because of vomiting, refusal to chew and refusal to open his mouth at mealtime.

He was the younger of two children. His sister, 9 years old, presented no difficulties. Birth history was normal, birth weight 7 pounds 3 ounces and weight at one year 23 pounds 12 ounces. He was breast-fed for ten weeks, fed with a spoon after that, had never taken a bottle but at 8 or 9 months used a cup for water. His milk was still spoon-fed. He used sentences, according to his mother, at 8 months, walked alone at 13 months, was trained for bowels at 5 months and for micturition at 9 months. There were no difficulties until after the first birthday.

The patient had been seen regularly by a pediatrician and was physically normal except for a somewhat receding lower jaw. An orthodontist who examined him suggested that this might account for his refusal to chew as he sometimes bit his lower lip. A second orthodontist noted the marked protrusion of the maxillae but stated that the molar relationship was good and the child could chew without difficulty.

At 2½ years the child was 34½ inches tall (within normal limits) and weighed 25 pounds 4 ounces, only 2 pounds more than at 1 year. All laboratory and x-ray examinations had been normal.

His mother reported that she strained all food and fed it to him with a spoon. If he liked it he opened his mouth a very little and allowed the food to be poured in, otherwise he clamped his jaws closed and a fight resulted during which his mother sometimes forced the food between his badly occluded teeth. Usually he spat it out at once. If a tiny lump was present in any food he vomited immediately after swallowing. His mother had tried to distract him by reading to him, playing with toys and singing, she had tried bribing with pennies and even dollars, she threatened with deprivation of privileges and spanking, and occasionally had struck him. Finally, about one year before, his mother had resorted to forcing. She used every technique to force him to eat what she felt was good for him. He was offered a well balanced, adequate diet.

The patient had never been away from his mother. She never went out at night and his sister was not allowed to take him outside to play. He had never been with other children (possibly because of his sister getting measles and his being very ill after injection of measles serum at the end of his first year). He did not dress or undress himself. He did not put away his toys. He was very aggressive toward his sister and appropriated her toys as he wished. He was demanding of his parents, hit his father when he tried to read his newspapers, refused to allow him to talk on the telephone and interrupted the conversation so continuously that his parents now had visitors only after he was asleep.

In the office he submitted willingly to a physical examination. He refused a lollipop. He was obviously bright and carried on a conversation demonstrating a large vocabulary. He demanded attention continually during the fifteen minutes following the examination when his mother was attempting to discuss his problems. Finally he announced he would vomit if his mother did not leave at once. She decided to go home and return another time without him.

This child is an extreme example of an overprotected, overindulged child. He was a wanted child—both children were wanted—but a boy would have been preferred when the sister was born. There had been a long wait of almost seven years before his birth. He was unusually bright and his parents adored him. At the end of his first year he had his only illness induced by a measure for which the parents felt responsible (injection of measles serum). His recovery and their feeling of guilt made him doubly precious.

His parents became concerned when he refused chopped food advised by his pediatrician. He had several teeth but his parents thought his malformed jaw might be the cause—the same reason given for his never taking the bottle. They waited several months. At about 18 or 20 months when the pediatrician again urged chopped and solid foods his mother became determined he should have them. Then the fight began.

The feeding difficulty here actually started when the parents spoon

fed their infant instead of teaching him to take the bottle. He remained immature in this respect and continued his infantile reaction by refusing solid foods and refusing to chew. This was intensified by his mother's continuing to feed him and not allowing him to use the spoon himself. He was dependent in other ways and had not developed self-reliance.

He was overprotected because he was a wanted child and because of the anxiety caused by his illness following injection of measles serum. During his second year he did not gain well and his mother used all known methods to get him to eat. This situation gave him a great deal of attention and he used it for his own ends. Being successful in this instance he insisted on prompt attention at all times and became aggressive and domineering.

The treatment is difficult. The parents have been reassured about his health and his malocclusion. They have been told that being bright he makes use of every weapon to gain attention but that this high intelligence can be turned into acceptable and gratifying pursuits. He can soon be taught to dress and undress, even to wash himself, he can do simple errands, he can be encouraged in outdoor play with other children away from his parents. With these satisfactions he will need less parental attention. And further, if the parents refuse to be concerned about his feeding difficulties the pleasure he derives from their anxiety will soon disappear. The first step is to let him feed himself food he is known to like—if he refuses he will eventually (perhaps after weeks not days) become hungry and start to eat. His parents must give up the idea that this or that is good for him and should be eaten. At the same time he must be reassured of his parents' love and be occupied with interesting activities. It is a long course but good eating habits are sure to develop.

THE EFFECT OF THE MATERNAL DIET ON THE INTRA-UTERINE FETUS

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THE rapidly growing bibliography on nutrition and pregnancy^{1 2, 3} attests to its increasing importance in the eyes of the obstetrician. Until a few years ago it was generally believed that most women in the average income group met the requirements for pregnancy and lactation when their usual diet was supplemented by 1 quart of milk daily, but recent work on large numbers of patients on supposedly normal diets has revealed inadequacies^{3, 4 5}. The accompanying table

THE BASIC MINIMAL DAILY DIETARY INTAKE FOR THE WOMAN IN PREGNANCY*

Dietary Element	Amount Required Daily
Protein	85 gm
Calories	2,500 calories
Calcium	1 5 gm
Iron	15 mg
Vitamin A	6,000 I U
Vitamin B ₁	600 I U
Vitamin C	100 mg
Vitamin D	400-800 I U
Riboflavin	2 5 mg

* Compiled by the Committee on Food and Nutrition, National Research Council, Federal Security Agency, Washington, 1941, G P O

lists the basic minimum requirements as set forth by the National Research Council⁶. Since the standards themselves are arbitrary, being made up from chemical tests on blood or excretory products which may or may not reflect the optimum level in the living organism, and since there are differences in metabolic rate and ability to absorb and store the various elements it must be emphasized that these are average figures and that changes are necessary to accommodate the individual needs.

We have reviewed the literature in an effort to clarify somewhat the status of the dietary factors which have been proved to affect

The opinions expressed herein are those of the authors and do not necessarily reflect those of the Navy Department.

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fetal growth, so that we may stress these factors to our patients rather than factors which are still in a questionable status

Factors of the Maternal Diet Proved to Affect the Well-being of the Intra-uterine Fetus.—From the work of Stuart,⁷ Macy⁸ and others there seems to be little doubt that the weight, length, vitality and rate of ossification can be favorably influenced by the amount of protein in the maternal diet. They find that intake of 85 gm of protein (of which a large portion should be of animal derivation) is optimum

Vitamin K, given to the mother in labor or in the last weeks of pregnancy, has been definitely shown to reduce the physiological hypoprothrombinemia of the newborn.⁹ Although the ability of this principle to prevent all types of fetal hemorrhagic diatheses has been grossly exaggerated, there is no doubt that those forms of hemorrhage due to or emphasized by hypoprothrombinemia are made less severe

The calcium-phosphorous-vitamin D relationship of the mother and infant has been recognized for many years, and while the burden of the decalcification is placed on the bones of the mother in instances of deficient intake of these substances, intra-uterine rickets is not unknown.¹⁰

Vitamin B deficiency as evidenced by maternal beriberi has been shown to produce an increased incidence of stillbirths and some of these fetuses were shown to have microscopic lesions compatible with the adult form of the disease.¹¹

There can be little doubt that vitamin E has a beneficial effect on a definite group of patients who are experiencing a threatened abortion. The clinical series, however, have been so poorly controlled and so heavily reinforced with other adjuvants such as bed rest, thyroid, progesterone and sedation that the exact value is obscure

Maternal Dietary Factors Suspected of Affecting the Well-being of the Intra-uterine Fetus.—The production of congenital eye defects in the experimental animal on diets deficient in vitamin A has been confirmed,¹² but there are no data at this time to show the importance of this factor in producing similar lesions in the human

It has been repeatedly demonstrated that iron plays a definite part in preventing and curing iron deficiency anemia in the maternal organism. Fetuses from these iron-deficient mothers are found to develop anemia within the first year of life although they are almost uniformly born with normal hemoglobin levels.¹³

Although vitamin C has been shown to be deficient in one type of capillary bleeding in the adult, there is no evidence that this element will protect the human fetus against any of the hemorrhagic conditions which afflict the newborn. The interesting fact has been brought out in the experimental animal that the mother with intra-uterine

DIABETES AND PUBLIC HEALTH

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RECENT investigations as to the prevalence of diabetes indicate the need of an active public health program with the triple aims of education, prevention, and early diagnosis. While the mortality from many other diseases, particularly those of infectious origin, has fallen within the last twenty years, diabetes has advanced to eighth place as a cause of death. Diabetes may be properly regarded as a public health problem affecting the welfare of the people.

The findings of the National Health Survey, based upon a questionnaire canvass made in 1935-1936 to determine the number of known cases of certain diseases, showed that approximately 3.67 individuals per thousand population were diabetic. More recently, investigations made by means of urine tests for sugar, indicated a much higher prevalence of diabetes than that suggested by the National Health Survey. Since case finding efforts uncover many latent cases and early diagnosis has been found to be important in the treatment of diabetes, the U. S. Public Health Service is now cooperating with medical and health authorities in developing a demonstration program which includes the finding of diabetes early, when it appears to be most amenable to aggressive scientific therapy.

A study to determine the number of known and unknown cases of diabetes is being made among a group of blind persons in Massachusetts. In view of the known high incidence of eye complications among diabetic patients, it seems logical by converse reasoning to expect a high incidence of diabetes among the blind. The Massachusetts Division of the Blind cooperating with the U. S. Public Health Service invited 1,968 blind people to have tests for the presence of the disease. Of this group, 883 have had postprandial urine and blood analyses for sugar. The positive findings are significantly high, 5.4 per cent being known diabetics, and an additional 3 per cent being diagnosed as a result of laboratory investigation. The newly discovered cases have been referred to physicians for confirmation of diagnosis and for treatment. This high incidence of diabetes among blind persons seems to warrant further investigation as to the relationship between the diabetic state and the ocular condition in this group.

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young is protected from the clinical picture of scurvy until delivery while the fetuses may be born with obvious lesions¹⁴

Maternal Dietary Factors Not Proved to Affect the Well being of the Intra-uterine Fetus.—There is no recognized standard level for fat and carbohydrate intake during pregnancy¹

The requirements for copper, cobalt and magnesium are recognized but deficiencies are unlikely⁸

The routine use of thyroid in physiological dosage has little to recommend it so far as the fetus is concerned. Thyroid feeding in large dosages to pregnant animals has been shown to produce fetuses which are thyroid deficient

Despite general opinion, there is no evidence to show that the baby is altered in weight, length or vitality by excess caloric intake so long as the diet is kept above actual starvation levels¹

SUMMARY AND CONCLUSIONS

For the rational instruction of patients with regard to nutrition during the antenatal course, we believe that these fundamental principles should be followed

- 1 The protein intake should be maintained at the level of about 85 gm per day. Individualization should not be sacrificed as to the patient's choice of food, and due consideration must be given to differences in weight of the patient, degree of activity, and medical indications for special diets

- 2 As weight gain should rarely exceed 20 pounds, fats and carbohydrates must of necessity be kept low to prevent obesity

- 3 In patients who tend to become hydremic, an effort should be made to limit sodium ion intake rather than water

- 4 Chronic constipation as a frequent condition during pregnancy should not be treated with mineral oil unless absolutely necessary because of probable interference with absorption of oil soluble dietary essentials

- 5 Iron and calcium at all times and vitamin D in the winter months should be given daily in the least expensive form in adequate dosage

- 6 Vitamin K can be utilized routinely during labor to reduce the occurrence of the physiological hypoprothrombinemia of the newborn

- 7 Vitamins C and E may be used where supplements are felt indicated but should in general be adequately cared for in the diet prescribed

- 8 None of these factors should be left to the imagination of the patient or to chance, they should be explicitly defined and specifically ordered in instruction sheets

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THE Rh FACTOR. ITS MODE OF ACTION AND CLINICAL RESULTS

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THE most recent and important advance in connection with blood transfusion is the discovery of the Rh factor in the blood. It is of importance because it concerns not only the obstetrician, pediatrician, transfusionist, hematologist and geneticist but also every physician whose patients may receive blood transfusions. Unfortunately, this subject was presented to the medical profession as distinct and separate from anything previously known. It came upon the profession with suddenness and considerable lay publicity so that at first confusion resulted. Although this discovery was important and new it simply heralded the birth of a new member of an already well known family. If we approach the subject from that point of view and recognize the principles involved, the entire matter becomes simple and understandable.

TRANSFUSION REACTIONS

Let us start therefore, with the known and proceed to the unknown. Everyone undoubtedly is familiar with the four blood groups, namely, AB, A, B and O. These four groups are determined by two agglutinogens or factors, the A and the B agglutinogens. The presence or absence of these factors determine the blood group. For example, if both are present the blood belongs to Group AB whereas if both are absent the blood belongs to Group O, and so on. In addition to agglutinogens in the cells, the sera of these individuals contain agglutinins. Each agglutinogen is specific and is able to react with a corresponding agglutinin thereby clumping the cells. For example, Group A blood contains anti-B agglutinins which agglutinate Group B cells, and the serum of Group O individuals contains agglutinins which react with both Group A and Group B. There are certain basic principles surrounding isohemagglutination. The cells must contain the factor or agglutinogen. The serum or plasma which causes the agglutination must contain agglutinins which are specific for certain agglutinogens. The agglutinins must be present in sufficiently high concentration or titer and there must be a definite proportional relationship between agglutinins and agglutinogens. These are the principles underlying post-transfusion hemolytic reactions. Such reactions are avoidable.

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When this was understood it was necessary that it be called to the attention of the general medical profession. It is of clinical importance to recognize that when blood of an incompatible group is given a patient, agglutination might take place. Under such circumstances, the transfusion would be followed by definite symptoms such as pain in the back and pain radiating down the legs. If sufficient incompatible blood is transfused, the pulse becomes rapid, thready and weak. There is dyspnea, cyanosis, perhaps pulmonary edema and even death. In certain instances, provided the patient survives the immediate effects, hemoglobinuria and anuria may develop.

As time went on, other agglutinogens or factors or characteristics of the red blood cells were discovered, namely, the M, N and P agglutinogens. The existence of these, however, was not called to the attention of the general medical profession because they were of little or no clinical significance. This is so because although the factors exist in the cells the corresponding agglutinins have been detected in the patient's serum only in an extremely few instances. Therefore, the conditions necessary for agglutination of the M, N and P factors almost never occur.^{1 2} These factors are inherited according to the Mendelian law, and knowledge in regard to them has important applications in cases of disputed parentage and is therefore important in forensic medicine.

Role of the Rh Factor.—More recently, still another agglutnogen was discovered, namely the Rh factor.³ Inasmuch as no anti-Rh agglutinins were found in the patient's serum it was thought that this factor would be relegated to the same category as the M, the N, and the P. Conditions necessary for hemagglutination did not exist and at first it was believed that this factor had no clinical application. Subsequently, studies on the bloods of patients who had developed hemolytic reactions following transfusion brought to light new information.^{4 5} Although the blood of both donors and patients were of the same A-B-O Group, they differed from each other in that the donors were Rh-positive whereas the patients were Rh-negative. Furthermore, the patients' serum contained anti-Rh agglutinins. It was concluded that, as a result of repeated transfusions, patients may become sensitized and develop anti-Rh agglutinins, and conditions necessary for agglutination develop. Under such circumstances further transfusions of Rh-positive blood result in hemagglutination and clinical results are the same as in cases of an A-B-O incompatibility.⁶ The only point of difference is that when the Rh factor is involved, agglutinins are produced by active immunization whereas, when the A or B factor is at fault, the agglutinins are preformed. Experience indicates that approximately one out of every twenty-five Rh-negative individuals possesses the constitutional ability to respond to exposure to Rh-positive cells (agglutinogens) by producing anti-Rh agglutinins. There is, however,

at present no method for detecting this in advance. Consequently, it is recommended for the sake of safety that only Rh-positive blood be given to Rh-positive patients and Rh-negative blood to Rh-negative patients.

RH FACTOR AND PREGNANCY

Subsequently, Levine and his co-workers⁷ described a second set of circumstances under which anti-Rh agglutinins can develop, namely during pregnancy. In one out of approximately twenty-five pregnancies, if the mother is Rh-negative and the father is Rh-positive and the fetus inherits this factor from its father, sensitization of the mother results. The factor passes from the fetal circulation through the placenta into the maternal circulation and stimulates the mother to produce Rh antibodies. Thus the mechanism is the same as when transfusions are given. If then, these newly developed antibodies pass through the placenta into the fetal circulation, various results may follow.

Before considering these results, however, it is necessary to understand that in exceptional cases there are different kinds of Rh-positive factors each of which produces a different kind of antibody (anti-Rh sera). As a result, instead of two types (Rh-negative and Rh-positive) there are eight Rh types. Understanding and remembering these becomes simple if the chart of reactions is built up in two stages. First, consider the factors which react only with two such anti-Rh sera (anti-rh' and anti-rh''). Four possible combined reactions are determined (Table 1, *b*). These two sera yield a chart with reactions identical with the reactions obtained with the anti-A and anti-B sera (Table 1, *a*). When, however, the reactions of a third anti-Rh serum, namely the anti-Rh₀, is taken into consideration, the four combinations become eight because either the four do not react to anti-Rh₀ serum (Table 1, *c*) or they do (Table 1, *d*). These eight possible combinations or Rh types^{8, 9} are named after the sera which cause the agglutination. Besides Rh agglutinogens, two Hr varieties, Hr' and Hr'' exist, which respectively can stimulate the development of anti-Hr' and anti-Hr'' agglutinins. The effects of these are identical with those of anti-Rh agglutinins. Serologically, however, they bear a relationship to the Rh genotype of the individual. For example, heterozygous individuals of type Rh₁ and rh' are Hr'-positive while homozygous Rh₁ and rh' individuals are Hr-negative. The recognition and understanding of these Rh and Hr types is important. Individuals have cells which contain factors which react positively to one or more antisera yet the same individual may lack other factors and react negatively to other sera (Table 1, *c, d*). For example, an Rh₁ individual is Rh-positive in that he reacts to the anti-Rh₀ serum, yet is negative when tested with anti-rh'' serum. Such an Rh-positive individual when exposed to the rh'' factor either by transfusion or pregnancy may develop anti-rh'' agglu-

tinus For clinical results to develop it is not necessary that the patient be negative to all the antisera ¹⁰

TABLE 1

NOMENCLATURE OF RH TYPES

(a) Four Possible Reactions with Anti-A and Anti-B Sera			(b) The Same Four Possible Reactions as in (a) Except with Anti-rh' and Anti-rh" Antisera		
Name of Cell Group	Anti-sera				
	A	B	rh'	rh"	
O	O	O	O	O	
A	+	O	+	O	
B	O	+	O	+	
AB	+	+	+	+	

(c) The Same Four Possible Reactions as in (b) But All Are Negative to Anti-Rh ₀				(d) The Same Four Possible Reactions as in (b) But All Are Positive to Rh ₀			
Name of Cell Type	Antisera			Name of Cell Type	Antisera		
	Rh ₀	rh'	rh"		Rh ₀	rh'	rh"
rh	O	O	O	Rh ₀	+	O	O
rh'	O	+	O	Rh ₁	+	+	O
rh"	O	O	+	Rh ₂	+	O	+
rh' rh"	O	+	+	Rh ₁ Rh ₂	+	+	+

Written in small letters, 'rh' denotes Rh₀ negative. When a capital letter is used it means that the Rh₀ factor or anti-Rh₀ agglutinin is present.

The reactions with sera indicated in Charts *a* and *b* are identical. Anti-rh' and anti-rh" are merely substituted for anti-A and anti-B.

Charts *c* and *d* merely repeat the four reactions shown in *b* but include the reactions to anti-Rh₀. In Chart *c* the reaction is negative to anti-Rh₀ serum in all cases whereas in Chart *d* it is positive in all cases. The Rh cell types in Charts *c* and *d* are named after the sera that cause agglutination of the cells.

When serum of a patient sensitized by the Rh factor following transfusion or pregnancy and in whom agglutinins have developed is mixed in the test tube with a 2 per cent saline suspension of Rh-positive cells, clumping or *agglutination* results. However, approximately half of all Rh-negative individuals exposed to the Rh₀ factor fail to develop demonstrable agglutinins yet when transfusion is given hemolytic reaction occurs and in cases of pregnancy the infant shows all the dire results that follow exposure to anti-Rh agglutinins. This puzzle too, was soon solved^{11 12} by the discovery of so-called blocking antibodies. Whereas agglutinins are bivalent and can link cells together (agglutination), blocking antibodies (blockers) are monovalent and simply coat the cells and ultimately hemolyze them but produce no visible clumping in the presence of watery solution (normal saline) (Fig 98). Even if serum known to contain anti-Rh agglutinins is added to cells coated with blocking antibodies, no agglutination results (hence the name "blockers"). If however, the watery solution is removed

and replaced with normal plasma or serum, another body, called protein, is introduced. This can make the coated cells stick together in clumps. This phenomenon is called *conglutination*¹³. These facts can be expressed as a formula, as follows

Rh-positive cells + Anti-Rh agglutinins = Agglutination

Rh-positive cells + Blocking antibodies = No agglutination

Rh-positive cells + Blocking antibodies + Anti-Rh agglutinins = No agglutination

Rh-positive cells + Blocking antibodies + X protein = Conglutination

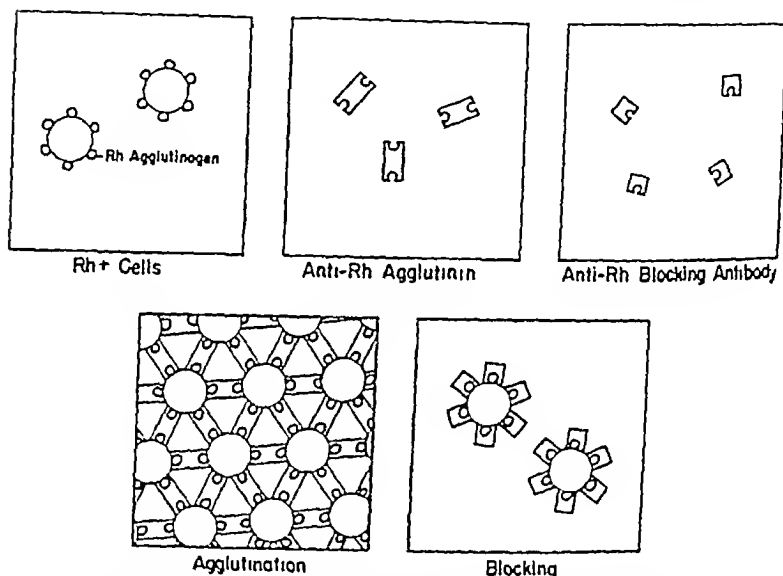


Fig 98 —Diagrammatic representation of Rh agglutination and blocking reactions.
(From Wiener, A S Am J Clin. Path, 15 106, 1945)

That certain mothers respond to exposure to the Rh₀ factor by producing either monovalent or bivalent antibodies or both is now thoroughly established. That they respond similarly with the production of rh' and rh'' blockers is possible. However, these two varieties up to the present have not definitely been found.

These are the serological facts that help us to understand the etiology of post-transfusion hemolytic reactions as well as that of erythroblastosis fetalis. The offending antibodies may be either the Rh variety (anti-Rh₀, anti-rh', anti-rh'', anti-Hr', anti-Hr'', Rh₀ blockers) A or B variety. In any case they act by clumping or hemolyzing erythrocytes which contain the corresponding factor. When one keeps in mind the different ways in which bivalent (agglutinins) and univalent (blockers) act in vitro, one would expect some difference in the result

as evidenced by the clinical picture in the infant. All of this is of importance because it becomes possible to predict, at least to a certain extent, by means of serologic studies *during pregnancy*, the condition that we will have to face. In addition, if the child is born alive, the appropriate treatment can be given and an intelligent prognosis made.

CONGENITAL ERYTHROBLASTOSIS

According to Wiener's theory,^{14 15} congenital erythroblastosis can assume one of three forms. Each form of the disease is predominantly caused by a different type of antibody. These three varieties will be described.

1 **Icterus Gravis Neonatorum.**—This is a condition due to intravascular clumping of the infant's red cells. Such clumping is most often caused by *bivalent anti-Rh agglutinins* present in the serum of the mother. Usually she is Rh-negative. It may occur, although rarely, in an Rh-positive mother who has developed agglutinins produced by exposure to the Rh or Hr factor present in the infant's blood but lacking in hers. During pregnancy such agglutinins can be detected in the maternal serum and the condition predicted. At birth the child may appear perfectly normal but jaundice develops within a few hours or days. Bivalent bodies are large molecularly and get through the placenta during pregnancy with difficulty, if at all. It is mainly during labor that the maternal blood is milked into the fetal circulation. For all practical purposes at the time of delivery, the child has received a transfusion of incompatible blood. The agglutinins clump the infant's cells with the formation of thrombi. Such thrombi lodged in the liver produce tissue damage and are a factor in the production of severe jaundice. Kernicterus may also result if thrombi are formed in the brain and the damaged ganglia secondarily become discolored.¹⁶ If such infants survive, they may show the results of cerebral damage. Cases of this type may also result from anti-A or anti-B agglutinins although such agglutinins are more often associated with *icterus precox*. While *icterus gravis* is predominantly a disease due to bivalent agglutinins, less frequently univalent antibodies in the mother's serum may be the etiological factor. Such cases are due to *in vivo* conglutination with results identical with agglutination. Table 2 illustrates these facts. It shows that of twenty-five cases of *icterus gravis*, bivalent antibodies were present in the maternal serum in sixteen, univalent bodies were found in eight, and in one case both were found.

If the condition is due to bivalent antibodies, exsanguination and replacement of the infant's blood with Rh-negative is the treatment of choice. The technique is relatively simple.¹⁷ Insert the needle for the transfusion into the saphenous vein at the ankle and expose the radial artery at the wrist. After 50 cc of blood has been transfused,

inject 0.2 cc of heparin intravenously, then nick the radial artery and allow blood to escape into a measuring glass. The transfusion and the phlebotomy should be so managed that the transfusion is about 50 cc ahead of the phlebotomy. When 100 cc of blood have been withdrawn, a second injection of 0.2 cc of heparin is administered and the transfusion continued until approximately 450 cc have been withdrawn and 500 cc given. At this stage, both processes are discontinued. The nick in the artery need not be repaired, as the bleeding can be controlled by a pressure bandage.

TABLE 2

CORRELATION BETWEEN THE QUALITY OF THE RH ANTIBODIES IN THE MATERNAL SERUM AND THE CLINICAL MANIFESTATIONS IN THE ERYTHROBLASTOTIC INFANT OR FETUS*

Nature of the maternal antibody	Type of Clinical Manifestation in Infant or Fetus		
	Stillbirths, No. of Cases	Hemolytic Anemia, No. of Cases	Icterus Gravis, No. of Cases
Bivalent (agglutinin)	2	7	16
Univalent (blocker or glutinin)	25	24	8
Bivalent and univalent (mixed)	4	10	1

* By A. S. Wiener.

Obviously it is impossible to replace all of the child's blood since, as the bleeding process is continued, more and more of the transfused blood is lost. When an amount approximately equal to twice the infant's blood volume has been given, approximately 90 per cent of the infant's blood has been replaced. To continue beyond this point seems profitless.

2 Congenital Hemolytic Disease.—This is a disease most often due to the action of *univalent or blocking antibodies* on the cells of the fetus during gestation. According to Wiener's theory these antibodies are smaller molecularly than the bivalent (agglutinins) variety and can therefore more easily traverse the placenta and gain access to the fetal circulation during gestation. By identifying them in the maternal circulation the result can in most cases be predicted. Having gained access to the fetal circulation, they attach themselves to and coat the erythrocytes which ultimately disintegrate. If the titer of these bodies in the mother's serum is sufficiently high an anemia develops and finally an hydropic stillbirth. If the titer of these bodies is

low the result is less severe and the child is born alive but anemic. Such children can be saved by proper transfusion therapy, and there are no sequelae.

Table 2 shows that congenital hemolytic anemia is predominantly due to univalent antibodies. Of forty-one such cases, in twenty-four univalent antibodies alone were found and in an additional ten they occurred together with bivalent antibodies. In seven of the forty-one only bivalent antibodies were demonstrable. In addition, in twenty-nine out of thirty-one cases of stillbirth, univalent antibodies were demonstrated in the maternal serum. However, cases in which the etiological factor was either bivalent anti-Rh, anti-Hr or A-B, agglutinins have also been observed, although rarely. If this condition is shown to be due to Rh₀ blocking antibodies and if at the same time there is a low grade anemia, blood transfusions of Rh-negative blood are to be recommended for the infant. These infants should also be well hydrated to prevent intravascular conglutination.

3 Icterus Precox.—Most of the icterus precox cases are due to A-B-O incompatibilities^{18, 19, 20} between the mother and the fetus although occasionally others may be due to the Rh or the Hr factors. If the mother's blood belongs to Group O, it has natural anti-A or anti-B agglutinins in it. The child, however, is normally protected against this. If as a result of this A-B-O incompatibility the mother develops a considerable increase in the titer of the antibody to which the infant's cells react, icterus precox can develop. A mild jaundice appears during the first few days of the infant's life. There is a mild degree of anemia from which the child will recover perhaps without treatment. These cases probably fall into the group of "physiologic icterus." On the other hand, the symptoms of erythroblastosis may be so severe that the child dies. Where the condition is of such severity that recovery is doubtful, intravenous administration of Witebsky's soluble A and B substances has been suggested.²¹ Transfusion of Group O blood with the plasma removed should be given if the indication of anemia exists.

Practical Problems.—In order to anticipate the outcome of a pregnancy the blood of the prospective mother should be examined, as soon as the diagnosis of pregnancy has been established. The correct procedure is to do a *complete Rh typing* not only on her blood cells but also on those of her husband to be certain that the latter's does not contain any of the factors lacking in the blood of the mother. The very minimum procedure, however, should be to determine whether or not the mother is Rh₀ negative. If she is Rh₀ negative, the blood of the father should be examined for this factor. In addition, the mother's serum *must always* be examined for anti-Rh agglutinins and Rh₀ blocking antibodies. This should be repeated monthly up to the seventh month, bi-monthly up to the eighth month and weekly thereafter.

A program has been inaugurated in Oxford, Massachusetts, with the aim of giving tests for diabetes to the 5000 residents of the town. At the present time, approximately 3300 people have received post-prandial tests of urine and blood. This study will furnish more reliable data than is now available regarding the prevalence of diabetes in a general population group.

A comprehensive preventive and control program is scheduled to begin in the next few months in Jacksonville, Florida. In a northern city, negotiations are underway for the establishment of a similar program. Tests for diabetes will be given not only to unselected groups representing a cross section of the population of the community, but also to groups believed most likely to have diabetes on the basis of clinical and statistical data, such as Jewish and Irish females over 45 years of age who have a history of diabetes in the family and are inclined to be obese. These programs, in addition to case finding, will emphasize dissemination of information to the public regarding the importance of preventing the disease, particularly among those susceptible by heredity and obesity. Personnel specially trained in diabetes will become a part of the staff of the local health department in each of these cities in order to assist in developing the programs.

All plans are formulated in cooperation with an advisory committee of the local medical society. Each newly discovered diabetic is referred to his family physician for further study and treatment. When requested by the medical practitioner, assistance in the education of his diabetic patients will be offered through the media of individual and class instruction in such subjects as variations and adjustments in diet, importance of hygiene, avoidance of complications and necessity of regular visits to the attending physician. This education would be given in clinical centers, hospitals, or special facilities provided by health departments.

Clinical research in diabetes is being encouraged as another part of the over-all program. A Metabolism and Endocrinology Study Section has recently been organized as a part of the Research Grants Division of the National Institute of Health for the purpose of stimulating research in this field. The Diabetes Demonstration Section also plans to investigate and possibly develop speedier and simpler methods of blood and urine analyses for sugar, since it is important that these tests be done at regular intervals in the care of the diabetic, and should be easily accessible to the attending physician.

in order to be in a position to anticipate the result of the pregnancy and to be prepared to give the appropriate therapy

Simply to determine that the mother is Rh-negative and that the father is Rh-positive is insufficient. The fact that she has developed antibodies must be established. Even though the mother is Rh-negative and the father is Rh-positive the constitutional ability to become sensitized exists approximately in only one out of twenty-five women. With few exceptions the first pregnancy is normal. The possibility of sensitization during the first pregnancy increases if the woman has been exposed to Rh-positive blood either by subcutaneous injection or transfusion. Once she has become sensitized, there is now no known method for desensitization and the condition becomes worse with each succeeding pregnancy. In spite of the sensitization, however, if the father is heterozygous, only 50 per cent of the pregnancies will be affected.

There is no known method to prevent Rh sensitization when the conditions necessary for its development exist. However, a course of vaccine therapy may be undertaken as suggested by Wiener.²² It is recognized that the efficacy of this treatment has not as yet been completely evaluated but since it is perfectly harmless, one is justified in resorting to it. It consists in giving biweekly injections of diluted typhoid vaccine in increasing doses for a period of six weeks, followed by a similar six-week course, substituting pertussis vaccine, and then returning to a course of typhoid vaccine. This treatment is based on the theory of competition of antigens. If an individual is exposed to two antigens simultaneously, it is hoped that the response will be to the bacterial antigen rather than the weaker Rh antigen. If the mother is a primipara, vaccine therapy is not indicated since the first born is almost never affected. In addition, if the mother's serum shows the presence of Rh antibodies, vaccine therapy is useless unless one administers it on the theory that an attempt should be made to prevent any increase in the titer beyond that already present.

If there is evidence of the appearance of, or increase in, the titer of Rh antibodies, cesarean section has been recommended as soon as a viable child can be obtained. The purpose would be to remove the child, as soon as it is safe, from the influence of the antibodies. At present it seems too early to take a definite position in this matter based on the serologic examination of the mother's blood. This is true for various reasons. If the father is heterozygous the infant may be Rh-negative and then will not be affected by Rh antibodies. The child may be hydropic and die, in spite of the cesarean section. In either of these two instances, the mother will have been subjected to an unnecessary operation. Infants have been observed who, in spite of the cesarean operation, subsequently became jaundiced. This has subjected the mother to the risk associated with a cesarean, and the

infant to the dangers associated with prematurity, yet the infant has developed the signs and symptoms of erythroblastosis. Until further information is obtained on this subject it seems wiser to avoid cesarean whenever it is not definitely indicated for other reasons and to rely on exsanguination and exchange transfusion in an effort to save the life of the infant.

Obviously the recognition of the Rh factor has created several practical problems. A rapid, simple method for determining the Rh factor and for providing an abundant supply of diagnostic sera was needed. This has been solved.^{23, 24} It also became necessary to maintain an adequate supply of Rh-positive as well as Rh-negative bloods. This, too, has been solved by the Medical Society of the County of New York through the establishment of the Blood and Plasma Exchange of New York. This is a cooperative nonprofit organization. Eight hospitals in New York with blood banks make their facilities available to all and furnish blood whenever needed. The blood bank of the New York Post-Graduate Hospital is the largest of the group and now has more than 60,000 donors annually. This large volume makes possible an adequate supply of Rh-negative blood at all times, which has been distributed throughout the United States and some parts of Canada. Several shipments of Rh-negative blood have been sent to Egypt and Turkey. Use of the airplane has expedited the distribution of blood to hospitals both near and far.

SUMMARY

The Rh factor should be viewed as a new member of the family of well known and well recognized hemagglutinogens. The chief point of difference is that anti-A and anti-B agglutinins exist preformed, whereas the Rh agglutinins do not. The latter varieties develop as a result of active immunization brought about either by repeated blood transfusions or by pregnancy. When Rh antibodies develop their effect on the Rh factor is identical to the effect of A or B agglutinins on the A or B factors. In either case, given the proper conditions, post-transfusion hemolytic reactions may result or during pregnancy erythroblastosis may develop. The former are avoidable.

Beyond this there are several refinements in connection with the Rh which must be recognized. There are several varieties of Rh and Hr antigens and as a result a number of different varieties of antibodies develop. These are the anti-Rh₀, anti-rh', anti-rh'', anti-Hr' and anti-Hr'' which are bivalent agglutinins, and Rh₀ blockers which are univalent antibodies. Certain women respond by the production of bivalent agglutinins whereas others develop univalent blocking antibodies and still others develop both kinds. Agglutinins tend to produce predominantly icterus gravis neonatorum whereas blockers tend to produce hemolytic anemia and stillbirths. The clinical condition is

influenced by the titer of blocking antibodies in the mother's serum. Low titers tend predominantly to produce hemolytic anemia, whereas high titers are in the overwhelming majority of cases followed by stillbirths. A and B agglutinins tend to produce icterus precox.

It is important to understand the difference in the results produced by these different bodies so that prenatally one can anticipate the result and be prepared to give appropriate treatment. To accomplish this it is necessary that the blood of the mother and father be examined as soon as the diagnosis of pregnancy has been established. Information that the mother is Rh-negative and that the father is Rh-positive, though important, is *incomplete*. The mother's serum should be examined at regular intervals for antibodies. The first evidence of the development of antibodies in the mother's blood should be a matter of concern in regard to the infant since this is the information which permits the prediction of erythroblastosis fetalis. Preparations should be made so that at the time the infant is born, exsanguination and replacement, with Rh-negative blood, of approximately 90 per cent of the infant's blood can be carried out. If no antibodies are formed although the conditions for sensitization exist, an attempt should be made to prevent their later development, by vaccine therapy.

At present, it seems unwise to advise cesarean section solely on the basis of the serologic findings. A plentiful supply of diagnostic sera for the determination of the Rh factor is now available and the technic for using it is simple and rapid. Large quantities of Rh-negative blood are necessary for proper therapy. The Blood Bank of Post-Graduate Hospital maintains such a supply and it is available wherever and whenever needed.

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SOME ENDOCRINOLOGIC ASPECTS OF RETARDED GROWTH AND DWARFISM

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DWARFISM, to many a practitioner, is a mere curiosity, an enigma to the ever-patient pediatrician as he predicts an unpredictable spurt of growth, and a challenge to the overzealous endocrinologist as he attempts to link alterations in skeletal growth with some childhood or adolescent endocrine disorder

The height of an individual is determined by the rate of growth and its duration. A slow rate of growth may be of prolonged duration due to delayed epiphyseal closure. The final growth, however, is usually subnormal. This condition obtains in various hypohormonal disorders.

Pronounced dwarfism occurs when retardation of growth is associated with normal or early epiphyseal closure. On the other hand, retarded growth, when accompanied by delayed sexual maturation, may allow growth up to normal stature and in some instances increased height or gigantism may be attained when duration of growth is prolonged. Therefore, retardation of growth does not necessarily result in diminished stature or dwarfism. Conversely, dwarfism is not necessarily due to a retarded rate of growth, for accelerated growth rate of too short duration, when associated with premature epiphyseal closure, may also cause dwarfism. Such instances are observed in cases of sexual precocity due to sex-hormone-producing tumors.

Accelerated growth frequently produces increased stature or gigantism if epiphyseal closure is markedly delayed. It is as yet a matter of speculation why the increased activity of sex hormones produces in some cases premature epiphyseal closure while in others inhibition of growth does not occur.

ETIOLOGY

The foregoing illustrates to a certain extent the effect of the endocrine system on growth. Numerous other causes, however, have to be considered and the classification of Shelton¹ although limited, particularly in respect to the endocrine factors of dwarfism, is worthy of mention.

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- 1 Inherent or constitutional factors—as in so-called primordial dwarfism and in normal small statured persons
- 2 Congenital disturbances of the skeleton—as in achondroplasia, mongolism and micromelic dwarfism
- 3 Anomalies of the circulatory and urinary systems—as in congenital heart and kidney disease, angioplastic infantilism and renal rickets
- 4 Disturbances of nutrition
 - 1 Inadequate food, vitamin and mineral intake—as in slow starvation, rickets and other deficiency diseases
 - 2 Inadequate absorption of the building essentials because of disturbances of the gastric, intestinal and pancreatic enzymes—as in hypochlorhydria, celiac disease, refractory rickets and intestinal nematodes
 - 3 Inadequate utilization or deposition of the essential elements because of various metabolic and endocrine disorders—as in hypothyroidism, hypopituitarism and diabetes mellitus
- 5 Chronic infectious disorders—as in tuberculosis and syphilis

In studying the dwarfed child, it must at all times be remembered that regardless of the category into which any single case falls, debilitating constitutional diseases and nutritional disorders, when they occur in childhood, may produce retarded stature with varying degrees of sexual infantilism. If this is kept in mind then the following would appear to be a simpler and more workable classification

- A Is the dwarfism *genetic*?
 - 1 Proportionate 2 Disproportionate
- B Is the dwarfism *hormonal*?
 - 1 Hypohormonal
 - (a) Hypothyroidism (b) Hypopituitarism (c) Hypogonadism (d) Diabetes mellitus (hypoinsulinism)
 - 2 Hyperhormonal
 - (a) Hypergonadism (b) Hypercorticotesteroidism.
 - 3 Nonspecific (as yet unclassified)

GENETIC DWARFISM

1 **Proportionate.**—This is known as true hereditary or primordial dwarfism. Such children develop into miniature adults. Mental and sexual development are normal. The centers of ossification appear at the normal times and epiphysal union occurs normally. There are no endocrine implications. Such dwarfism may occur sporadically in normal families and is hereditary in certain races. In legend this group is exemplified by the Lilliputians.

2. **Disproportionate.**—Achondroplasia is usually a sporadic disorder but may be hereditary. It is due to abnormal bone function during fetal life. The clinical characteristics are very short extremities with bowed limbs and large feet. The abdomen is prominent and there is apparent lordosis, due to a tilting forward of the sacrum. The face is usually small, the head large and the hands show fingers of equal lengths (Fig. 99). If such children survive the first year they show

marked virility with a strong muscular system. Statural retardation results primarily from developmental faults in the osseous system.

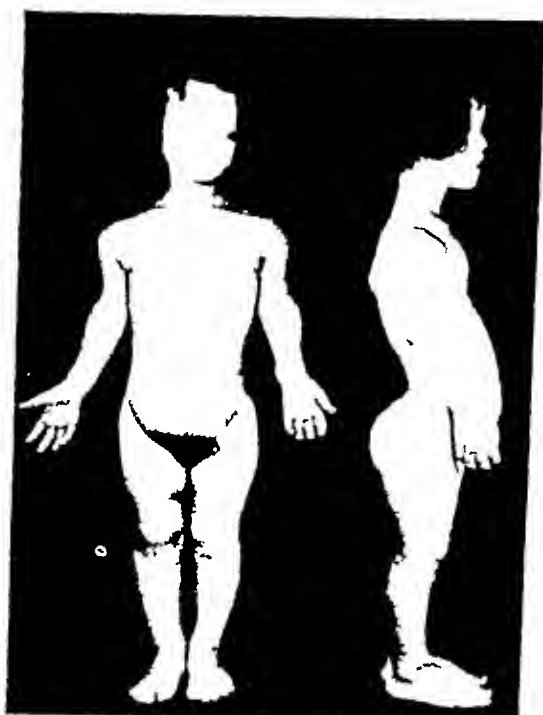


Fig. 99—Achondroplastic dwarfism in a girl nine years of age (Courtesy of Dr. H. H. Turner.)

HORMONAL DWARFISM

1. **Hypohormonal.**—(a) **HYPOTHYROIDISM**—(1) *Cretinism*—Stunted growth, retarded osseous development and mental retardation are prominent features of this condition. Subnormal metabolism is readily evident in such cases by the slow pulse, subnormal temperature, thickness and coldness of the skin, pallor of the cheeks and lips and a tendency toward adiposity. A high level of serum cholesterol is strong confirmatory evidence in diagnosis.

(2) *Juvenile Hypothyroidism*—The clinical picture differs from that of cretinism in the milder degree of symptoms. Usually there is a history of normal early growth and development followed by an abrupt or gradual retardation. The patient who shows retardation of growth in adolescence, when associated with suggestive symptoms of hypothyroidism, should have the benefit of complete x-ray studies and laboratory tests and the specific response to thyroid therapy.

(b) **HYPOPITUITARY DWARFISM**—(1) *Panhypopituitarism*—This is

a state in which somatic and sexual development are arrested some time before puberty through a deficiency in the anterior pituitary hormones. The classical case is characterized by a small statured but well proportioned body with all the features of a child retained through adolescent and adult life (Fig 100). At a relatively early age

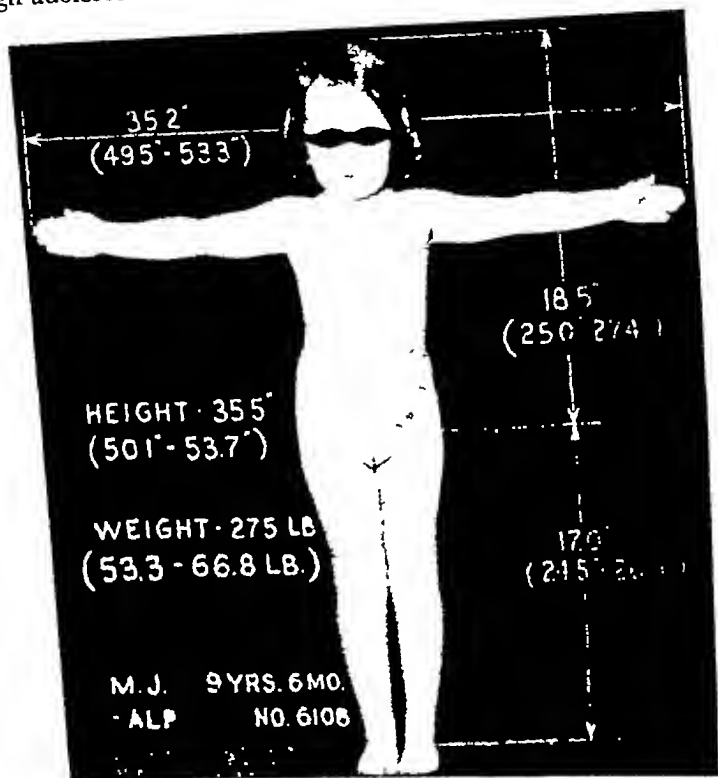


Fig 100—Pituitary dwarf, 9½ years old (Reproduced from *Endocrine Medicine* by W Engelbach, through courtesy of the publisher, Charles C Thomas, Springfield, Illinois)

in adolescence, the skin becomes dry and wrinkled giving the individual a wizened, owlsh appearance. Sometimes they present definite senile features originally described as Gilford's progeria^o or *nanisme*.

• Premature old age (progeria) with dwarfism (nanism) may be seen in contradistinction to panhypopituitarism. Recently two brothers, aged 17 and 19 years who presented all the signs and features of progeria with nanism, were studied. Premature closure of all the epiphyses was noted. The dwarfism was marked, the features of senility profound, the bone age tremendously advanced, simulating the bones of elderly individuals. Sexual retardation was not present. The disorder is thought to be heredofamilial in nature due to a germ plasma defect. These patients differ from the patients with panhypopituitarism who show some mild symptoms of premature aging.

senile de Variot.^{2, 3} Other characteristics are small hands and feet, narrow fingers and soft, silky hair. The sexual infantilism is marked. Pubic and axillary hair are usually absent. Breast and genital development are minimal. The ossification centers appear late. The epiphyses remain open well into adult life. The basal metabolic rate is below normal. The pituitary fossa is usually small and bridged.

(2) *Lorain-Levi Syndrome*—Lorain's infantilism, originally ascribed to malnutrition and hereditary influences, was linked to pituitary disease by Levi in 1908. It is essentially the type described under "pituitary dwarfism" without signs of progeria and is usually due to pituitary damage. Obesity is usually absent. The most common cause of pituitary damage responsible for this syndrome is a craniopharyngioma. Symptoms of headache, vomiting, progressive loss of vision, weight loss and diabetes insipidus may be present. The most consistently positive clinical signs are primary optic atrophy, papilledema, hemianopsia, positive Macewen's sign (cracked-pot resonance) on percussion of the skull. Roentgenograms of the skull show calcification above and in the sella turcica.⁴

(3) *Selective Hypopituitarism with Secondary Hypogonadism*—These patients are somewhat stronger and usually taller than true pituitary dwarfs. In the female there is lack of development of the breasts, vagina and uterus. The most striking characteristic is the complete absence of pubic and axillary hair, suggesting not only an estrogen but also an androgen deficiency. The bone age is retarded and the epiphyses often never unite. Gonadotrophins are below normal and the excretion of 17-ketosteroids is low. Estrogenic therapy fails to bring about increase of pubic and axillary hair. The following case history is of interest.⁵

CASE I—J K was a bright little girl, aged 23, with sexual infantilism and decreased stature. Physical examination revealed a short, pudgy, healthy looking girl without pubic or axillary hair and with undeveloped breasts, vagina and uterus. Her height was 60 $\frac{1}{8}$ inches and the span was 57 $\frac{1}{2}$ inches. A castrite smear and pH reaction of 8 were obtained on study of the vaginal secretions. Assay of the blood gave a negative test for prolactin and 17-ketosteroid determination yielded 2 mg for a twenty-four hour specimen of urine. Blood calcium and phosphorus values appeared disturbed. The disturbed ratio of 15 to 38, however, was gradually restored to the normal of 10 to 38 after the second month of therapy. Basal metabolic rate, blood pressure, glucose and insulin tolerance tests were within normal limits. X-ray studies of the right elbow, hand, lumbar and thoracic spine revealed marked delay in the fusion of the epiphyses of the bones of the wrist and hand. Views of the right elbow show delay of union of the epiphysis of the inner condyle (Fig 101). The other epiphyses had united. The lateral view of the skull showed no erosion around the epiphyses and no intracranial calcification. Suture lines of the skull appeared within normal limits. Lateral film of the thoracic and lumbar spine showed developmental defects of the bodies of the epiphyses.

The past history revealed that at the age of eleven the patient had a menstrual

show of blood which lasted a few minutes. She never menstruated again although she often had attacks of low pelvic (uterine) cramps at monthly intervals. During the past ten years she had had several courses of oral estrogens and each year, during her seventeenth, eighteenth and nineteenth year, had received a course of fifteen to twenty injections of antuitrin-S. These were without apparent benefit. At the age of 13, the patient's height was 52 inches, and during the following ten years she grew $8\frac{7}{8}$ inches. In her family history, it was learned that her father was six feet tall and her mother five feet two inches tall. A diagnosis of sexual infantilism due to selective pituitary deficiency was made.

The patient has been under treatment for almost two years and menstrual bleeding has been induced regularly from the second month of treatment onwards.



Fig 101 (Case 1)—Selective pituitary failure with secondary hypogonadism in a girl 23 years of age. Note delayed closure of the epiphyses.

At first this was accomplished by the cyclic administration of estrogens and progesterone. Bleeding ensued a few days after the withdrawal of therapy in every instance with the exception of the first trial. The parenteral administration, in divided doses, of about 100,000–150,000 I U of estrone or its equivalent followed by 40 to 50 mg of progesterone proved adequate. Normal smears and pH reactions of the vaginal secretions were obtained after the fifth day of estrogen therapy (total dosage of 50,000 I U of estrone). Later, to reduce the cost of therapy, oral estrogens (one tablet daily of 1.25 mg of estrone sulfate or 0.5 mg of estradiol) followed by a course of 30 mg of anhydrohydroxyprogesterone per day for five days, proved equally successful.

To reduce the cost of therapy further, stilbestrol 0.25 mg per day, was sub-

THE AMERICAN DIABETES ASSOCIATION

CECIL STRIKER, M D , F A C P *

In discussing diabetes, it is essential to recognize that the ultimate goal is the benefit of the individual diabetic. Heretofore, most monographs have devoted pages to the technic of clinical and experimental problems involved. While it is true that the diabetic is the essential consumer of the benefits of this knowledge, the maximum benefit must include other factors such as medico-economics, public health aspects, socio-medical factors, and a host of other nonspecific but equally important considerations such as a united organizational interest.

In view of this, it is pertinent to discuss the history and activities of the American Diabetes Association and to relate what responsibilities it proposes to accept for the future.

In 1937, a group of physicians met to consider the formation of an American Diabetes Association. In 1938, there were five known local diabetes organizations, these were situated in Cincinnati, Detroit, New York City, Philadelphia, and Rochester, New York. Official representatives of the known existing societies met and drew up plans for the formation of a nation-wide organization. A formal constitution was adopted and the Association was incorporated in the state of Ohio as a nonprofit organization in 1940. The first meeting was held in Cleveland, Ohio on June 1, 1941. This meeting was attended by over three hundred physicians from various parts of the United States and it devoted itself to the scientific phases of diabetes.

Subsequently, there has been a scientific meeting annually and in the course of these deliberations, various committees have rendered their reports. Always the interest and activities of these groups have been aimed at the advancement of the diabetic patient. Since it has been in existence, the Association has been mindful of its prime responsibility, which is the improvement of the patient. It has studied various problems such as "quack remedies," improvements of insulin, establishment of summer camps for diabetic children, statistical investigation to ascertain more information concerning the prevalence and

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stituted for twenty days each month and withdrawal bleeding followed just as readily. Cyclic interruptions with occasional courses of oral progestins were interspersed every few months in order to simulate physiologic conditions as much as possible. Thyroid therapy, $\frac{1}{2}$ grain per day, was instituted for varying periods of time. During the period of observation there occurred a marked improvement in the bodily contour and genital development (Fig 102). The patient's outlook and interest in life matured. Growth has continued at its own rate. From May 12, 1943, to January 6, 1946, she grew $2\frac{1}{4}$ inches in height.

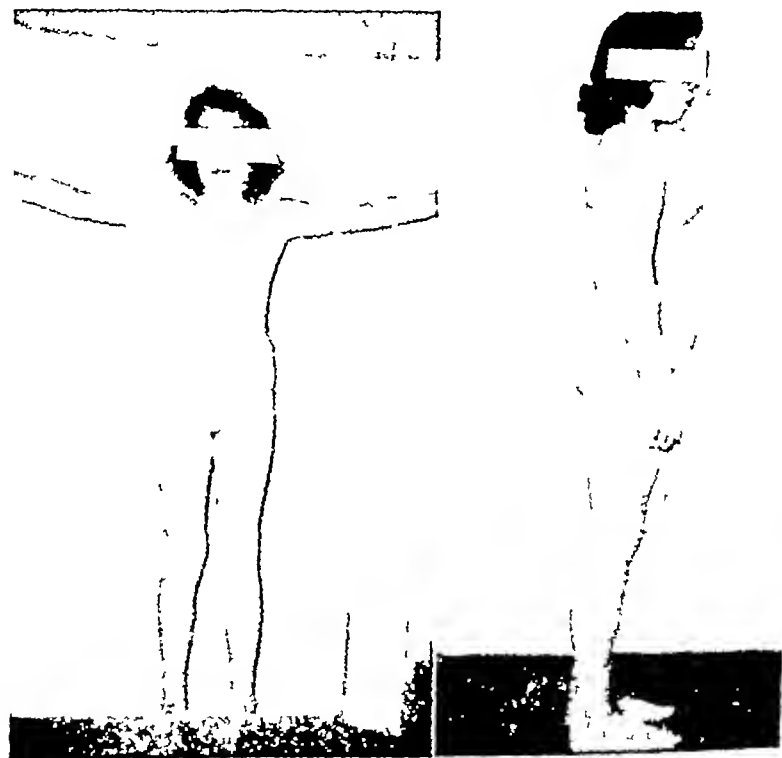


Fig 102 (Case I) —Before and after treatment with sex steroids. Note marked sexual infantilism. After estrogen-progesterone therapy excellent breast development and improvement in bodily contour occurred. After androgen therapy pubic hair appeared.

Recent x-ray of the right elbow and hand two and one-half years after the start of steroid therapy revealed closure of the inner condyle of the humerus and of the epiphyseal lines of the metacarpals. Retarded union of the epiphyses of the radius and ulna was still present (Fig 103).

Excellent development of secondary sex characteristics occurred following estrogen-progesterone therapy. However, sexual hair failed to appear. In order to stimulate growth of sexual hair three short courses of testosterone propionate in 10 mg. doses totaling 60, 90 and 120 mg. respectively were tried at various periods of time. There soon followed a growth of fine pubic hair. Encouraged by

this show of hair, two intensive courses of methyl testosterone were administered orally at monthly intervals in doses of 30 mg per day for twenty-one days. Definite growth of pubic hair resulted.

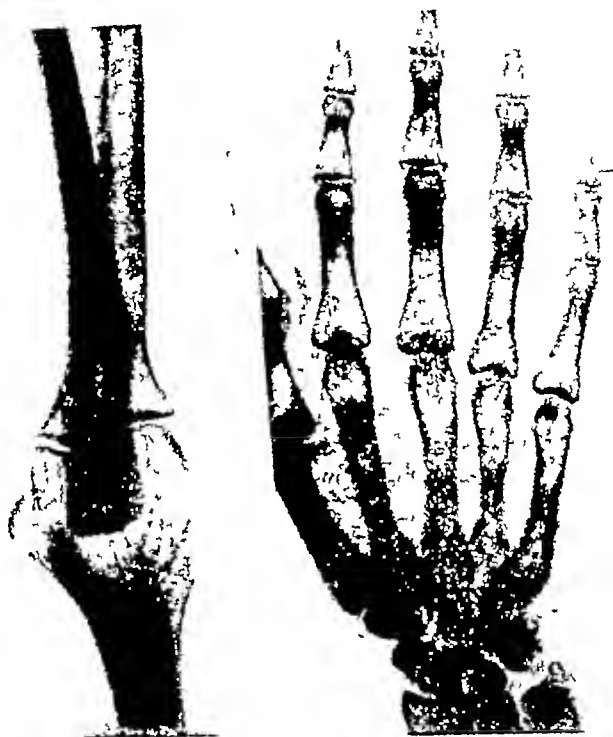


Fig 103 (Case I) —Two and one-half years later, after many courses of the steroid hormones. Note closure of the inner condyle of the humerus and epiphyseal lines of metacarpals but retarded union of epiphyses of radius and ulna.

The findings in this case do not follow the pattern of panhypopituitarism but do fit a diagnosis of selective pituitary deficiency. Sexual infantilism with decreased stature may result from deficiency of pituitary gonadotrophins in cases in which some or all of the other functions of the pituitary remain undisturbed. To account for the absence of pubic and axillary hair in this patient it may be assumed that there was probably a deficiency of one of the fractions of the corticotrophin factor. The lack of ovarian hormones is readily explained by a deficiency of secretion of the gonadotrophic factor. The syndrome in this patient does not fit in with a diagnosis of so-called primary ovarian dwarfism (*vide infra*).

(c) HYPOGONADAL (PRIMARY) DWARFISM —In the female, ovarian deficiency is frequently associated with the specific features of the ovarian dwarf. Short stature is associated with a lack of development

of the breasts, vagina and uterus and the absence of the menarche. Pubic and axillary hair are either absent or scanty in amount. Congenital anomalies like webbing of the neck and coarctation of the aorta are frequently present. Precocious senility may occur. The roentgenogram may reveal osteoporosis and late union of the epiphyses. Vaginal films show lack of cornification and glycogen deposition. Gonadotrophins are usually increased and 17-ketosteroids are usually decreased but not minimal.

There are some distinctive differences in the clinical picture and possibly the laboratory data, depending on whether ovarian deficiency



Fig 104 (Case II) —Delayed bone age in girl of 14 years with ovarian dwarfism.

is of primary nature or secondary to failure of the pituitary to produce the gonadotrophic factors necessary for ovarian stimulation.

Specific types of hypogonadal dwarfism and their treatment will now be described.

(1) *Primary Ovarian Dwarfism or Albright's Syndrome* —The main characteristics which distinguish this syndrome of sexual infantilism with dwarfism from that due to pituitary failure are the short stature rather than dwarfism and the presence of pubic and axillary hair although in reduced amount. Administration of estrogenic preparations results in increase of axillary and pubic hair while no such effect is obtained in the presence of pituitary failure. These individuals are usually quite strong and well nourished and their bone ages are only

slightly retarded. There is usually an increase of follicle-stimulating hormone in the urine⁶⁻⁹. It is, however, not certain that lack of deficiency of ovarian function will result permanently in excessive excretion of gonadotrophins. Normal amounts of gonadotrophin excretion were reported in a girl castrated at the age of 12 and in patients with proved ovarian agenesis¹⁰. The 17-ketosteroids are decreased but not to a minimum and the insulin tolerance test shows normal hypoglycemia responsiveness. Cystic areas in bones and atrophic changes in the vertebrae may be found and a fairly marked degree of hypertension may be present.⁹ Additional congenital anomalies like coarctation of the aorta and webbing of the neck are occasionally encountered.⁸

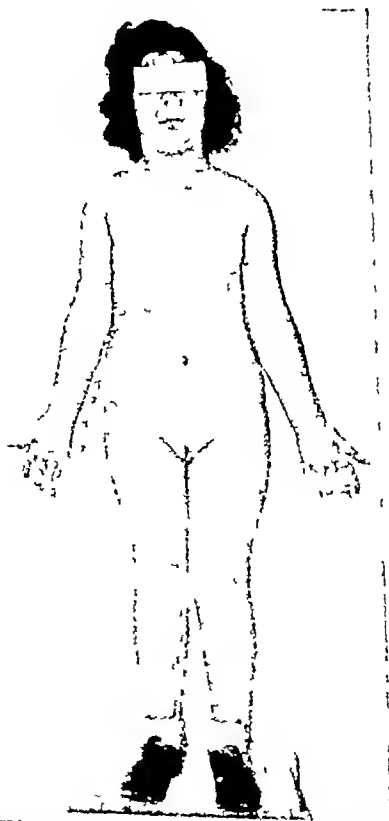


Fig 105 (Case II) —Note scanty pubic hair in a well developed girl of 14 years with diminished stature, diagnosed as ovarian dwarfism. Photograph taken two months after estrogen and thyroid therapy.

CASE II —L. W., a girl of 14 years of age, when first seen was 51½ inches in height. She was of stocky build, with dry skin and dull facial expression. There

was some hair growth on the arms and legs and very scanty growth of pubic and axillary hair. Vaginal smears were immature. The menarche had not yet occurred. Roentgenograms of the sella turcica showed no erosion and the right elbow, forearm and hand showed delayed bone age (Fig 104). X-ray of the spine revealed slight osteoporosis. The patient was placed on $\frac{1}{2}$ grain of thyroid daily and was given estrogen therapy for the first three weeks of each month. On her second visit two months later her height had increased to 52 $\frac{3}{8}$ inches. Improvement in her well being, alertness and breast development was noted (Fig 105).

(2) *Turner's Syndrome*—Turner described seven female patients aged 15 to 23 years with retardation of growth and sexual development.¹¹ Additional signs were congenital webbing of the neck, a low posterior hair margin, increase in the carrying angle of the elbow and cubitus valgus (Fig 106). The roentgenogram showed demineraliza-

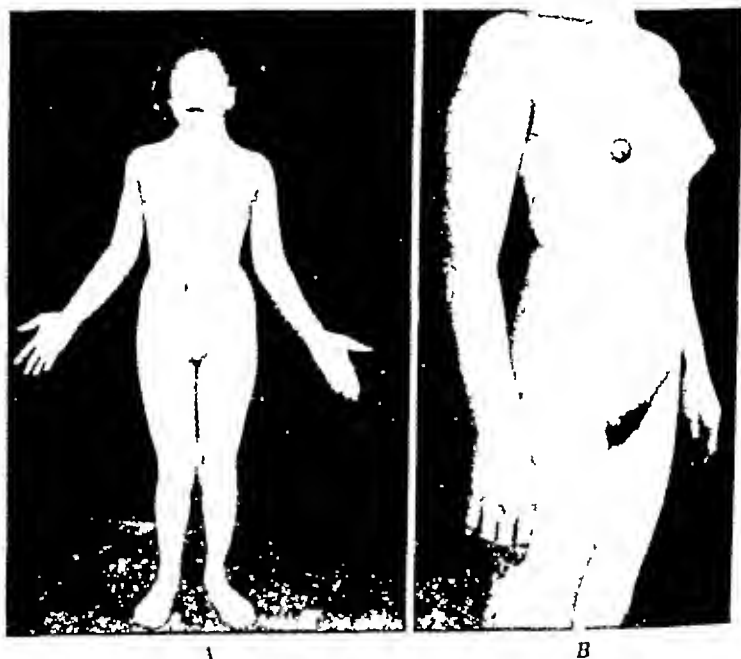


Fig 106—A, Turner's syndrome. Note webbing of neck, increased carrying angle, scanty pubic hair and lack of breast development in a girl 21 years of age. Height 53 inches, weight 78 pounds. B, Same patient after estrogen therapy. (Courtesy of H. H. Turner.)

tion and evidence of delayed union of the epiphyses in six cases. Treatment with pituitary growth hormones was unsatisfactory. However, following administration of the anterior pituitary gonadotrophic hormone, there was definite improvement in the cases so treated.

No gonadotrophin determinations were made and it is not quite

clear whether this syndrome is associated with primary ovarian deficiency or with partial pituitary failure. Recent evidence,^{6, 8, 12} however, points to the fact that Turner's syndrome is accompanied by a primary ovarian deficiency. Shereshevski described in 1925 a patient which he considered as pituitary dwarfism with additional unusual deformities and later added five more cases.³ Their characteristics are essentially those described by Turner. In addition to retardation of growth, Shereshevski's cases showed hypogenitalism or malformed genitals, delayed development of secondary sex characters, spaced, carious teeth, high palate, deformed helixes and aplasia of fingers and toes in some. Abundant hair growth on head which sometimes extended below the base of the neck was observed. The facial expression was older than the chronological age and was made strangely immobile by the presence of thick folds of skin extending from the base of the skull to the shoulders on both sides of a short neck. The basal metabolic rate was uniformly normal and other clinical and x-ray examinations showed nothing of special note. Progress in school was poor in two and satisfactory in three. Shereshevski suggested that signs of hypophysial dwarfism and sexual infantilism may be secondary to a pineal disorder.

(d) **Hypoinsulinism (Diabetes Mellitus)**—Retardation of growth and sexual development not infrequently occur in diabetes mellitus. In all probability the resultant nutritional disturbance is responsible for the delayed skeletal and sexual growth, since adequate control of childhood diabetes with insulin and diet usually allows for the normal progress of growth and sexual development. Ultimate decreased stature may result if treatment of the diabetes is delayed too long.

2 **Hyperhormonal Dwarfism**—(a) **Hypergonadism**—The excess secretion of steroids (estrogens or androgens) is a stimulus to statural growth. Premature closure of the epiphyses, however, may lead to ultimate dwarfism. Granulosa cell tumors in young females result in precocious puberty and an early spurt in skeletal growth. Testicular tumors in young males, though exceedingly rare, may produce similar results, i.e. precocious puberty and dwarfism.

(b) **Hypercorticotesteroidism**—Adrenal cortical hyperplasia or tumor in childhood gives a syndrome in the female of hypergenitalism characterized by hypertrophy of the clitoris although some enlargement of the uterus and vagina may also occur. Heterosexual sex characteristics may be present. In the male the typical "infant Hercules" is the classical example. Adult strength and sex development along with abnormally rapid osseous development and premature fusion of the epiphyses cause cessation of growth before adult height has been attained.

3 **Nonspecific or Unclassified**—The cases of primary ovarian dwarfism most frequently encountered are those described by Al-

bright Not infrequently, however, there are patients with diminished stature and some mild degree of ovarian deficiency who do not fall in the category of any of the above described syndromes The following two cases were selected as examples of the variety of symptoms apparently of endocrine nature associated with stunted growth The common characteristic of these cases is diminished stature with premature epiphysial closure Sexual hair was either normal or somewhat increased

CASE III—A. B., a white girl 16 years of age, complained of amenorrhea, hot flushes, dizzy spells, headaches, weakness and failure to grow She was a well nourished, obese girl, 55 $\frac{3}{4}$ inches in height, with a span of 52 inches The expression on her face was older than for her age She had graying hair on the head and pubis, vitiligo on the forehead and axilla. The head was well developed and



Fig 107 (Case III) —Poor breast development with moderate growth of pubic hair in girl of 16 years with premature closure of most of the ossification centers

the extremities were short. She had poorly developed breasts which increased in size with estrogen therapy Pubic and axillary hair were moderate The carrying angle of her arms was increased (Fig 107) She was mentally alert and, in fact more mature than her years There was a disproportion in growth of her fourth and fifth fingers and toes in relation to the second and third fingers and toes (Fig 108) Webbing of the second and third toes was present

The family history revealed vitiligo on the forehead and axilla in the mother, webbing of the second and third toes in her grandmother and niece On examina-



Fig 108 (Case III) —Note disproportion of 4th and 5th fingers and toes of hand and foot to 2nd and 3rd. Webbing of 2nd and 3rd toes was also present.



Fig. 109 (Case III) —Premature closure of the epiphyses of elbow and hand. Note disproportion in size of 4th metacarpal. Epiphyses of radius and ulna still open.

tion of the patient, an infantile vagina with an immature vaginal smear was found. Her eyegrounds showed slight tortuosity of vessels (few areas of arteriovenous compression). The blood pressure was 132/80 (prone) Roentgen studies of the

right elbow and right wrist showed premature union of all the epiphyses except the radius and ulna (Fig 109) Lateral view of the lumbar and sacral and lower thoracic spine showed similar premature fusion X-ray of the skull showed no definite erosion around the sella turcica, with premature fusion of the suture lines of the skull The roentgenogram of the right ankle showed premature epiphyseal closure including the metatarsals Premature fusion was also seen on x-ray of the knee Her excretion of 17-ketosteroids was 7.7 mg per twenty four hour specimen of urine

Estrogen therapy alleviated the hot flushes, headache, dizziness and weakness and produced estrogen withdrawal bleeding

CASE IV—I R, a 17 year old white female, complained of diminished stature, irregular menses, nervousness, and premenstrual headaches She was always small for her age and at the age of 11 years she started to put on weight and almost ceased to grow in height Menarche occurred at 13 years Menses were regular for about two years and then the interval increased to three or four months between periods She has now become completely amenorrheic

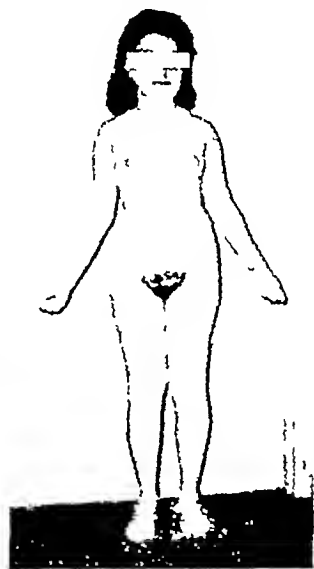


Fig 110 (Case IV) —Note well developed breasts and heavy pubic hair Since this photograph was taken three years ago, patient has developed mild facial and bodily hirsuties

Her height was 55½ inches and the span was 54½ inches The body weight was 118½ pounds She had a moon shaped face Exacerbation of acne occurred with each menses The trunk was short The breasts were well developed, firm and symmetrical She had an increased carrying angle of the arms heavy feminine pubic and axillary hair and mild hypertrichosis of the abdomen, thighs and face (Fig 110) Pelvic examination showed the external genitalia moderately reddened and somewhat infantile the introitus admitted only one finger and the cervix was small and conical The uterus was rather small Her basal metabolic rate was minus 1 The blood pressure was 105/70, the pulse 80 Roentgen studies of her left hand and right elbow showed premature epiphyseal closure (Fig. 111)

Blood chemistry studies revealed no abnormalities. Recently blood titers of follicle stimulating hormone and urinary assays of 17-ketosteroids were performed and the levels for both were markedly increased. At first, treatment consisting of thyroid, $\frac{1}{2}$ grain twice a day, produced regular menses. Ammonium chloride, $7\frac{1}{2}$ grains three times a day, was prescribed for relief of premenstrual headaches. Now that secondary amenorrhea has set in, menstrual bleeding is produced only following estrogen withdrawal therapy.



Fig. 111 (Case IV) —Premature union of all epiphyses in a girl 17 years of age

COMMENT

The close association of stunted growth with ovarian insufficiency in certain types of dwarfism suggests a possible role of estrogen deficiency in the genesis of dwarfism. Albright³ discussed the possible causes of stunted growth associated with ovarian agenesis and concluded that changes in growth are not likely due to a direct effect of estrogens on the epiphyseal cartilage. That primary ovarian deficiency leads to secondary changes in the anterior pituitary which in turn interfere with the production of growth hormone by the hypophysis is ruled out on the basis that castration in males does not lead to decreased stature in spite of the fact that the same overproduction of follicle-stimulating hormone in the pituitary takes place. This objection may not be altogether valid since castration in the male causes an

complications of diabetes, and in the early period of the war, the creation of identification tags for diabetics which could be used in the event of catastrophe. Furthermore, it has considered the question of establishing lay diabetes societies in which the problems of the patients could be discussed in their own meetings, with consultants such as physicians and other scientists who are interested in this disease. During the war, it was felt by the Association that no attempt should be made to establish such lay organizations but an energetic program has been activated and committees of the Association are now actively at work and, in due time, specific programs and projects will be announced.

Recent studies of rejected selectees revealed an extremely high incidence of glycosuria. Further studies must be made to determine whether these rejectees who have sugar in their urine are suffering from diabetes or whether glycosuria is due to factors other than diabetes. A special committee of the American Diabetes Association has been working on this problem and one report has been published in the official proceedings of the Association.

Much interest has been manifested in and great results were accomplished by the British Diabetes Association. During the London blitz, when it was difficult or impossible for diabetics to obtain insulin or get their meals at a specific time after their injections of insulin, the British society established emergency cards which were authorized by the British government so that the diabetic could obtain his insulin injection or food or first aid at hospitals and depots, so there would not be unnecessary delay in obtaining needed attention. Furthermore, through the British Ministry of Health, diabetics were able to obtain special rations so that they could regulate their diets even in wartime.

In this country, too, we were prepared for such an emergency. Identification tags were prepared and distributed to physicians who in turn could pass them out to their patients so that, in an emergency, the first aid station would immediately be made aware of the diabetic state. Many complications would have been prevented in this way. Furthermore, an officer of the American Diabetes Association was appointed a member of the Subcommittee on Medical Food Requirements of the National Research Council, the organization which advised the Office of Price Administration on food rationing for special medical dietary needs. Thus, diabetics in this country were in necessary instances given extra food ration points so that they could regulate their diets.

In several instances, the Federal government has had the aid of

increased activity of both basophils and acidophils. Furthermore, hypogonadism in the male leads usually to excessive height and eunuchoidism. It may be conjectured that the absence of estrogen due to ovarian deficiency causes increased basophilic cell activity. This in turn produces a decrease in the acidophils which supposedly secrete the growth hormone. In addition the estrogen-androgen balance may be disturbed toward a relative increase in androgens which probably cause premature closure of the epiphyses with stunted growth as in Case IV. On the other hand, the lack of estrogen deprives the adrenal cortex of one of its powerful stimulants. Thus its activity may be decreased and androgen production lowered. This probably occurs in those cases of ovarian dwarfism associated with marked androgen deficiency.

Albright suggests that the absence of the stimulating effect of estrogen on the adrenal cortex and the subsequent decreased adrenal cortical function may be responsible for stunted growth. The reduced excretion of 17-ketosteroids in these conditions is in favor of this assumption. The possibility, however, that decreased stature has nothing to do with ovarian hypofunction and that both are the result of some widespread defect in the organism is strongly suggested by Albright. The frequency of other congenital anomalies supports this hypothesis.

TREATMENT

Therapy of dwarfism should be directed towards the correction of the underlying cause, and growth is possible as long as epiphysal union has not occurred. In relation to endocrine therapy the nutritional factor is perhaps one of the most important in the treatment of retarded growth.

Growth Hormone—The pituitary growth hormone on the whole has given very unsatisfactory results. Its frequent administration and possible antihormone formation make its application at this time undesirable. Although a pituitary growth preparation may in some cases produce slight growth, it will, when administered alone, never restore a dwarf to anything near to normal height, since growth is the effect of combined pituitary, thyroid, adrenal and gonadal activity. Shelton¹ reports only one instance in which, he considered, the patient grew as a result of the administration of anterior pituitary extract.

Thyroid.—Thyroid therapy is indicated in those cases which show signs of thyroid deficiency. Otherwise, its application appears to be valueless, although it is claimed that the thyroid enhances the result of treatment with pituitary growth hormone.^{14, 15} The cretin and the juvenile hypothyroid dwarf show remarkable response to thyroid medication. Dosage should be relatively small to start with (1 gram per day) and increased gradually to 3 or 4 grains per day.

Treatment of Dwarfs with Primary Hypogonadism.—In females with ovarian deficiency the rational treatment consists of substituting ovarian function with either estrogens or estrogen-progesterone therapy. Estrogens may be administered orally as estrone sulfate in doses of 1.25 mg daily, estradiol 0.5 to 1 mg daily, or stilbestrol 0.25 mg daily for twenty-one days and resumed seven to ten days later or after bleeding has occurred and ceased. If progesterone is given in addition, the estrogens are administered as above, followed by progesterone in the form of anhydrohydroxyprogesterone, 100 to 150 mg in divided doses for five to six days. Under such therapy withdrawal bleeding may be expected. The breasts develop rapidly up to a certain point. Their shape may be cylindrical rather than the normal conical shape. The uterus may grow to nearly normal size and the vaginal epithelium shows rapid proliferation and maturation. Vaginal films show a full estrogenic effect. The bodily form becomes more shapely and feminine.

In male dwarfs the treatment of choice is the administration of androgens in the form of testosterone propionate, 10 to 25 mg three times per week intramuscularly, or in the form of methyl testosterone, 10 to 25 mg per day administered perlingually or orally.

Dwarfism Associated with Partial Pituitary Deficiency and Secondary Hypogonadism.—The treatment of choice in this condition would be substitution therapy with growth and gonadotrophic hormones. The administration of growth and follicle-stimulating and luteinizing hormones has, however, given poor results and the same treatment as outlined for dwarfism associated with primary hypogonadism is indicated in these cases. In cases of dwarfism in which the absence of pubic and axillary hair also indicates an androgen deficiency, methyl testosterone, 10 to 25 mg daily sublingually in addition to estrogens should be administered in courses of one or two months followed by intervals free from androgen therapy^{5, 10}. Such treatment causes an adolescent spurt of growth similar to that produced with androgens in hypogonadal male dwarfs¹⁸. The cited doses of androgens do not yield signs of virilization.

In males with dwarfism due to partial pituitary deficiency a better growth-promoting effect is obtained if androgen administration is combined with gonadotrophin therapy¹⁰⁻¹⁸. Several courses of chorionic gonadotrophin are given in doses of about 500 I U two or three times per week for eight to ten doses with a one month rest interval between courses. This therapy induces retention of nitrogen, inorganic phosphorus, sulfate and calcium and promotes temporary retention of sodium chloride and water.

The administration of hormonal preparations is contraindicated in achondroplastic dwarfs as well as in cases of dwarfism associated with hypergenitalism due to a granulosa cell tumor or adrenal cortical

hyperfunction or tumor Needless to say, it is futile to administer hormonal medication if roentgenograms reveal closure of the ossification centers

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OBESSE THYROIDPITUITARY DEFICIENCY IN THE MALE

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ONE year ago I presented in this Journal a paper on obese thyroid-pituitary deficiency in the female, which I regarded then, as I do now, as a distinct category of hypopituitarism¹

The condition is characterized by a triad of signs and symptoms which include obesity, hypogonadism (menstrual disturbances in the female), and signs and symptoms of pituitary deficiency. The obesity may be slight, the genital involvement difficult to evaluate, and the associated symptoms of various degrees, influenced by temperament, by the compensatory mechanism of the body, and by a total lack of uniformity. It was concluded from the uniform and predictable results of therapy by means of desiccated thyroid and a water-soluble extract of the anterior lobe of the pituitary body that, in spite of variabilities encountered, obese thyroid-pituitary deficiency is a distinct clinical entity. In that report fifty-two female patients were presented and the results of the treatment of all three phases of the triad were tabulated.

At this time I am presenting my clinical experience over a period of eight years in treating a group of patients from whom twenty-seven have been chosen for this report primarily because they cooperated well and were treated for a sufficiently long time to warrant therapeutic evaluation. All of these males were obese, had symptoms of gonadotropic inadequacy, and suffered symptoms associated with hypopituitarism. Their age and weight ranges are given in Table 1.

TABLE 1
AGE AND WEIGHT RANGES

No. of Patients	Age, Yrs.	Weight, Lbs.	Average Weight, Lbs.
5 Adults	35-45	167-227	191
3 Youths, definitely under average height (see case histories)	11 5-12	82-104	95
19 Youths over average in height (see Table 2)	6-20	75-239	157

The number of male *adults* seeking treatment for their obesity was fewer by far than the number of females since the male is much less

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concerned with his appearance than is the female, paying little attention to the cosmetic effect of obesity. He found it difficult to stay away from his work in order to come regularly for treatment and when he did come it was usually for a reason other than his obesity. The complaints were usually fatigability, dyspnea on the least exertion and occasionally disorders of the sexual function, frequently he complained of anginal pains. Male *juveniles*, on the other hand, were greater in number than the adult males or juvenile females, due to obvious sexual underdevelopment. They were referred to us generally for treatment of their sexual underdevelopment and statural undergrowth, mental and/or physical sluggishness, prolonged juvenility, and, in some instances, behavior problems.

SIGNS AND SYMPTOMS

Obesity.—Any overweight was considered obesity if it was associated with other signs and symptoms of the triad. As a rule the typical pituitary deposits were obvious. However, *gain in weight* was considered more significant than actual overweight. Weight gain was usually continuous but, too often, intermittent periods of stationary weight had lulled the patient into a feeling of security until a new increase, perhaps of tremendous proportion, had shattered his contentedness into recognition of an unpleasant reality.

Hypopituitarism.—This subject was discussed at length in my report on female patients with hypopituitarism¹ and repetition is not in order here. What has surprised me is the extreme state of fatigability, debility and the number of headaches that a male will endure before reporting for an examination. The reason is his fear of being told that he is "sick," making it necessary to stop work. Anginal pains with negative cardiac findings were frequent. The severest symptoms occurred when efforts to compensate for physiological deficiencies were unsuccessful. Severe discomfort with no apparent pathologic findings often produced neurotic, even psychoneurotic manifestations. There were more symptoms by far in the obese male who was financially insecure than in the few persons without money worries.

The young patient has no sense of obligation and develops few symptoms. Occasionally, when pressed too much by disciplinary measures at home or at school, behavior problems are produced. The histories of many of the patients in our series revealed an obvious regression from high scholastic levels.

Gonadotropic Inadequacy.—Few adults complained specifically of sexual debility. Many were loathe to admit it, some were too generally debilitated to be aware of it, and many used their "fatigability" as a prop for their inferiority. The anxiety of the parents of boys with "undescended testes" or underdevelopment of the genitalia was ex-

treme Some of these parents, when asked whether they had ever seen testes in the scrotum of their boy during a bath, answered spontaneously in the affirmative, surprised to recall that they had seen them on many such occasions However, a close examination of many of these boys revealed that the testes actually were underdeveloped Even those which were occasionally discovered in the upper part of the scrotum disappeared at the least touch due to an active cremasteric reflex Once drawn up toward and beyond the ring, they were not seen for long periods of time This active cremasteric reflex, often present with testes of relatively normal development, was our criterion of mild underdevelopment when associated with other signs The sexual organ buried in loose mons fat could not be too easily measured In general, the penis was classified as "relatively small," "small" or "infantile," the testes, according to size, if discovered, the scrotum was classified as "smooth," "flat" or "loose and roomy" The cremasteric reflex was carefully evaluated because changes in degree, without resorting too much to manipulation, denote progress or regression

Natural Growth.—Boys who were smaller than average gave their parents considerable concern, especially when "shortness" was a family trait In answer to parents' anxious questions, we would agree that "smallness" was inherited but that in many cases growth could be influenced simultaneously with correction of *other* interrelated physiologic deficiencies Unfortunately, no figure could be obtained of previous rates of growth Measurements at school or in camp are too frequently taken with shoes on, or otherwise carelessly, to be reliable An estimation of bone age was undertaken roentgenographically, when indicated

Laboratory Data.—Basal metabolic estimations are poor criteria of thyroid involvement Some were high, many were within normal range, and others frankly were low¹ Repeated estimations are necessary when one studies children High estimations did not prove to be contraindications to thyroid therapy, even in children who were nervous and irritable Clinical trials with small doses of thyroid extract often supplied the "go ahead" signal for such treatment, following which the metabolic rates were found to be lower

Blood Chemistry—Moderate anemia and slightly increased uric acid estimations were often noted In many cases, however, the blood chemistry figures were found to be of little diagnostic value

Roentgenographic Studies—In very young persons the carpal ossification centers were frequently retarded This finding was more consistent than the low basal metabolic rate In the older child (13 to 15 years), though bone age was usually retarded, some of the shorter children revealed early closure of the epiphyses with cessation of growth in spite of a *relative or actual hypogonadism*

THERAPY

Treatment consisted of diet, desiccated thyroid by mouth and anterior lobe pituitary extract by intramuscular injection. To avoid possible confusion when evaluating therapy and because no individual symptom in any of our patients in this series was considered important enough to merit it, no other therapeutic measures were adopted than those about to be described.

Diet.—A diet high in protein, moderate in carbohydrate and low in fat content was prescribed for all patients in this series. However, strict adherence to a limited calorie diet was hardly to be expected from our clinic patients. The importance of regular eating, no eating between meals, and limitation of the salt and water intake (where indicated) was stressed. The directions were as simple as possible and attempts were made to "teach" proper eating, a measure to be maintained even after a patient was "cured."

Medication—Desiccated thyroid by mouth—1 gram daily—was prescribed. In the presence of an unchanged pulse rate or of a pulse rate below 90, the dosage was increased by 1 gram every two weeks until an elevated pulse rate or subjective symptoms indicated that the point of tolerance had been reached. When counting the pulse rate of children special care was taken to avoid confusion that might be caused by rushing to the office, or other signs of excitability. A water-soluble unfractionated extract of the anterior lobe of the pituitary* was used, 1 cc being administered intramuscularly three times each week. If the patient was extremely obese or had a puffy, bloated appearance, we added 0.3 cc, of posterior lobe extract (obstetrical pituitrin) which was increased by 0.1 cc at each dose until tolerance (intestinal rumbling or cramps) was reached. If the patient could not maintain a dose of at least 0.5 cc, obstetrical pituitrin was discontinued.

If hypertension and/or precordial pain accompanied the obesity, all medication was given with great care, and increased cautiously.

RESULTS

Response to therapy has been evaluated on the basis of improvements or alterations in *each phase* of the complaint. In general, improvement followed the pattern described in the female.¹ Specifically, the accompanying case histories, charts and illustrations give all necessary details to demonstrate the *response* to therapy. There is little to add in cases of the male adult (Table 3). The youngsters changed in appearance within six to eight weeks, they looked taller and slimmer long before material loss of weight or increase in height took place (Fig. 112, a, b, c, Fig. 113b). All the more remarkable were the

* Most of the material used throughout this work was the preparation, "Water Soluble Extract Anterior Pituitary Substance," from Armour Laboratories, Armour & Co., Chicago, Illinois.

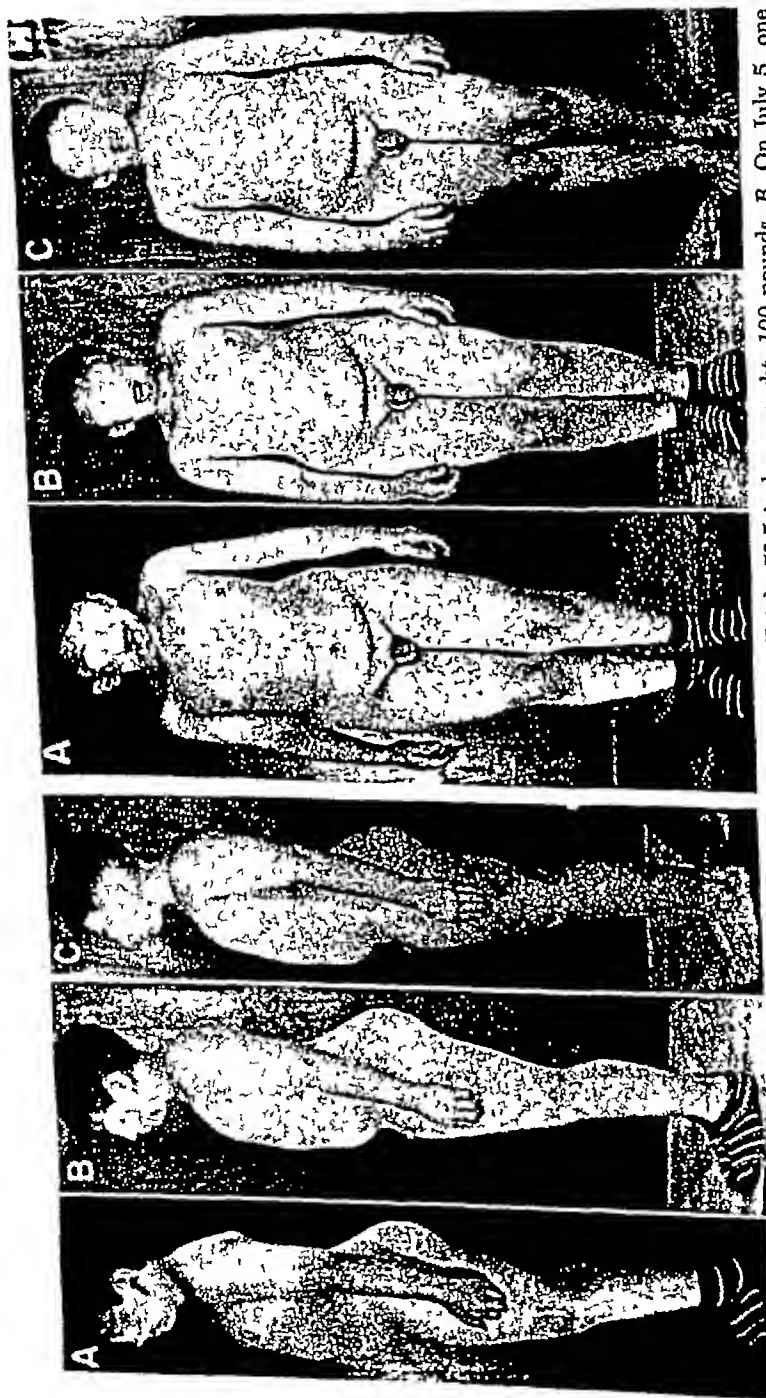


Fig 112 —A, Patient on June 5, 1944 at the beginning of treatment Height 53.5 inches, weight, 100 pounds B, On July 5, one month later Height, 54.1 inches, weight, 97 pounds C, On August 4, two months later Height, 54.5 inches, weight, 100 pounds.

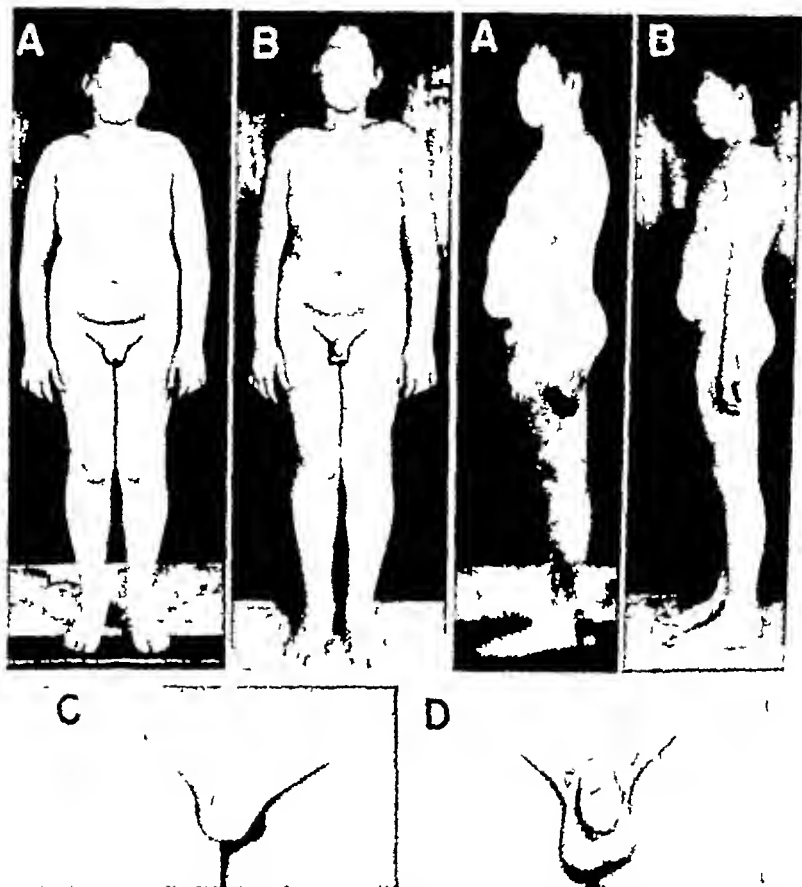


Fig 113 (Case G F, Table 2) —A, At beginning of treatment. B, Five months later C, At beginning of treatment D, Fourteen months later



Fig 114 (Case F R. B1367, Table 2) —At beginning of treatment and six months later

genital changes (Fig 113, *b*, Fig 114) Close watch was disappointing at first, but before long the flat scrotum, a mere faint discoloration in the perineum, became a dependent sac Testes, at first seen only occasionally and migrating beyond reach with the slightest stroke over the inner thigh, soon were detected at every examination, increased in size, merely bobbing slightly in response to the cremasteric reflex Genital organs seemed to emerge from the deep niche of mons fat

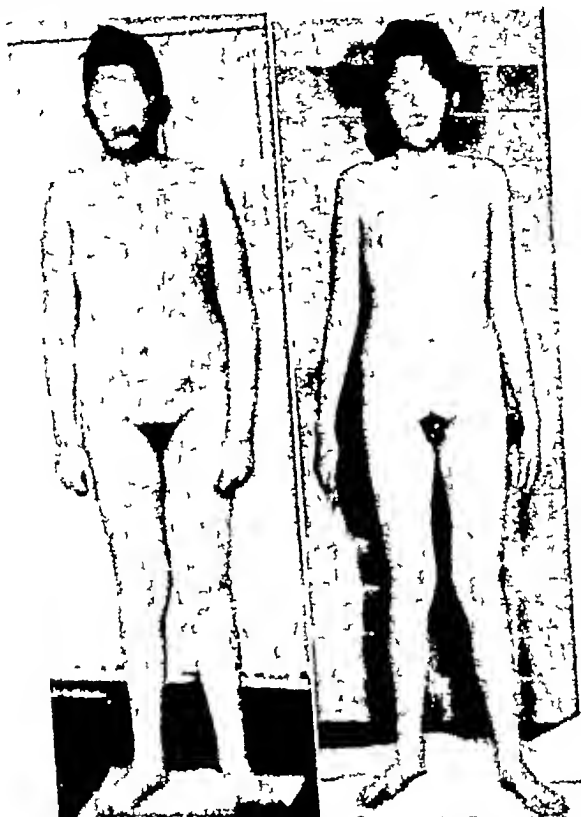


Fig 115 (Case M H B3588, Table 2) —At beginning of treatment and ten months later Genital response considered inadequate

All these changes took place within a few months without recourse to chorionic gonadotropins or testosterone Fat deposits disappeared with or without weight loss and height increased, the weight remaining the same or decreasing Enuresis, when present, was controlled and physical activity increased while behavior and general school work improved Occasionally, changes were slow to occur and even unsatisfactory So predictable were our results, however, that this slow response, especially in regard to the genitalia, made us suspect a pre-

members of the American Diabetes Association in prosecuting manufacturers of useless diabetic remedies

The American Diabetes Association has over nine hundred members. They reside in the United States, Canada, Denmark, England, Central and South America, India, Australia, Iceland and many other places. Thus its influence is global in nature.

Twenty-five years ago Dr. Frederick G. Banting and Charles H. Best, working in the laboratory of Professor J. J. R. Macleod at the University of Toronto, isolated the substance of the pancreas that had the ability to lower the blood sugar and control and enable a depancreatized dog to survive for an indefinite period. Their first report was presented at the University of Toronto, Physiological Journal Club, Room 17, on November 14, 1921, at four o'clock. The speakers were Drs. Banting and Mr. Best and the subject was "Pancreatic Diabetes." The first two papers reporting the results of their work were published in February, 1922 and May, 1922 in the *Journal of Laboratory and Clinical Medicine*, Volume 7. The official titles were "The Internal Secretions of the Pancreas," page 251, and "Pancreatic Extracts," page 464. Since these original publications, there have been over twenty thousand articles written concerning the experimental and clinical uses of insulin in addition to which there has been an unfolding of a new experimental era in carbohydrate metabolism.

In view of the great significance of the facts just presented, a commemorative meeting under the joint auspices of the University of Toronto and the American Diabetes Association was held on September 16, 17 and 18, 1946 at Toronto, Canada. This meeting brought together almost all the men interested in the field of diabetes. It was extremely unique, in that the only missing members of the earlier workers in the field were Sir Frederick Banting and Professor J. J. R. Macleod. Among some of those in attendance were Professor C. H. Best, Professor J. B. Collip, Drs. Walter R. Campbell, Russell M. Wilder, Seale O. Harris, Elliott P. Joslin, Rollin T. Woodyatt, as well as Dr. R. D. Lawrence of London, England, Dr. H. C. Hagedorn of Gentofte, Denmark and Dr. D. A. Houssay of Buenos Aires and a host of others long interested in the field of carbohydrate metabolism. This meeting attracted over five hundred physicians from all parts of the world. The first day was under the aegis of the University of Toronto and was devoted to a commemorative exercise. The Chancellor as well as the President of the University of Toronto and the Premier of the Ontario Provincial Government were among the participants. The second and third days were under the aegis of the

TABLE 2
ONSET THYROIDITIS DEFICIENCY IN THE JUVENILE TO ADOLLESCENT MALL

Case	Age	Total Period Observed (months)	At Start and End of Observation Wt (lb.)	Normals (Langbeach)		Signs and Symptoms	Course and Follow up
				Average for Age Wt (lb.)	Maximum Wt. for Actual Height (lb.)		
1112 L. W.	6	16 1	98 49.5 87 53	11 15 53 10.2	59.8 71.6	Referred for 'undescended testes' however, discovered on occasions the hyperactive cremasteric reflex causing them to disappear. I suggested abdominal mass, fat, sluggish mentally and physically, 'rats' and drinks a great deal, gaining weight rapidly	Genitalia improved within the 1 month of treatment testes descended well and reflex (cremasteric) became less active Did not return to clinic up to end of 16 month period
1171 H. S.	7	15 5	75 19.6 88 53.7	18.6 17.2 50.6 51.2	59.8 71.5	Short, stocky sluggish mentally and physically testes barely discovered in fat, scrotum smooth and flat they are lax and does not play with others Gaining weight rapidly	Treatment irregular during the 2 years Genitalia improved during first 6 months became more active and almost under regular observation for additional 4 years all fat deposits gone normal Genitalia Age 13 wt 124 lb 61.5, normal ave 114.58.9, wt 85.1
1175 L. G.	9	7 3	109 51.7 95 55.8	58.6 51.2 61.6 52.2	78.5 82.1	I noticed small undeveloped genitalia testes not discovered chest, girdle, abdomen obesity Gaining weight rapidly	Testes scrotum and genital organ normalised, disappearance of fat deposits, anorexia cured almost and improved in school
118 N. H.	10	9 2	93 53 80 51.5	51.9 53.2 7.2 55.2	71.6 77.5	Nervous untires and restless all the time Gaining weight rapidly Night testes discovered on occasions left testes undescended They had treatment for years Gain in weight is recent	General nervousness and stunting much improved Through treated previously both testes in scrotum neither disappearing with scrotal reflex Gained 7 lb in last 2 months refused additional treatment
1180 C. P.	10.5	21 11	114 57.5 151 62.8	68.1 54.2 8.2 57.1	87.2 111	Hidradenae almost mutually, poor school work shoulder abdomen pelvic girdle and mass obesity large mammary fat deposits, genital organ almost completely buried in mass fat testes pea size and drawn beyond reach by active cremasteric reflex	General improvement in every respect Note relative loss of weight, better from school reported better work all signs of pituitary obesity gone pubic hair of 12 tests low in scrotum normal size Did not return to clinic
118 J. H.	10.5	12 2	112 58 129 61	70.2 54.7 7.8 57.1	91.5 105	Parents concerned about underdeveloped genital organ Chest still mass thigh obesity gaining weight rapidly Genital organ buried in mass fat testes relatively small and migrate rapidly on slight excretion stimulation well behaved and very good at school	Genitalia improved in 2 months no further treatment deemed necessary during regular check ups fat deposits disappeared Further check-ups for 2 years—no regression

111111 A H	11	30 11	124 111	62.5 60.5	72 89	55.2 59.0	110.7 139	Gaining weight and growing rapidly in height. Testes not discovered, chest abdomen slightly thick obesity. Shipped thin to age 5 gained after tonsillectomy	Gain of weight stopped more active and alert lost weight testes and genital organ improved but not enough (See Fig 115) Chlorotic gonadotropin did not help Left eline and gained weight again
111111 A W	12	1 1	127 120	55 56	78 82	57.1 50	79 83	Short sighted obese, thin in age 8 gained after tonsillectomy typical baby face undeveloped genitalia buried in mons fat. Testes very small occasionally discovered. Headaches	Headaches disappeared became more active and alert testes increased in size genital organ no longer buried in mons fat Did not return to clinic
111111 A W	12	4 1	146 125	58 59	78 80	57.1 57.5	71.6 97	Child, abdomen mons thick obesity genitalia fairly well developed polydipsia polyphagia, thin to age 6 gained after tonsillectomy, head aches and gets out of breath easily	Improved generally school report better Does not get out of breath no headaches returned from summer vacation with gain of 12 lb Refused additional treatment Not seen since
111111 A V	12	20 20	158 163	58 62	78 93	57.1 60.7	91.3 111	Difficult irresponsible with generalized obesity, exaggerated fat deposits about chest abdomen genitalia mons and thighs Genitalia completely hidden by mons and thigh fat, testes discovered with difficulty migrate actively with scrotal reflex, home cooperation poor inactive and poor in schoolwork no home control	Poor cooperation and progress was slow genital development improved to normalcy report from school told of definite improvement fat deposits disappeared tall-tale story of lumps evident Left eline and gained 15 lb
111111 F H	12	7 2	109 116	58 59	78 85	57.1 59	91.3 90	Growing rapidly and gaining weight since appendectomy two years ago, scrotum flat and smooth, left testis not discovered genitalia relatively small, sella turcica reveals bridging clinoids	No cooperation with diet genitalia however improved, scrotum increased in size as did testes (See Fig 114) both equal in size and extent of descent. Craniostatic reflex normal Fat deposits gone
A H	12	8 6	122 116	58 60	78 82	57.1 58	92 101	Dyspnea nervous, undescended testes thin to age 3, gained after tonsillectomy now gaining weight rapidly genital organ well developed but buried in mons fat generalized obesity with exaggerated elbow, abdomen mons and thighs testes not discovered approximated clinoids over sella turcica	Gain of weight stopped, dyspnea no longer a complaint, activity increased some improvement in genitalia but not sufficient. Not seen since
111111 F	13	3 2	135 129	61 62	85 86	58.9 59.1	105 111	Bright, intelligent gaining weight rapidly, especially over pelvis, glands, abdomen and mons, clinoids approximated eyes puffy, palpebral fissure small, gets tired easily, genitalia relatively small	Gaining no longer loss of fat deposits with increase of palpebral fissure changed appearance, active and no longer complains of fatigue
111111 A C	13	22 18	161 169	60.5 62.4	85.4 101	58.9 62.4	103 113	Large, difficult to handle poor cooperation at home, generalized obesity with pituitary exaggerations genital organ small, testes pea size with active scrotal reflex headaches, poor work in school, sluggish physically	Poor cooperation at home, genitalia appear normal with pendulous scrotum and well descended testes, wide flare of lips evident in spite of absence of former fat deposits. Warned in regard to care and follow-up but did not appear for a year, wt. 205, ht. 65

TABLE 2—Continued

Case	Age	Total Period Observed Time Treated (months)	At Start and Last of Observation Wt. (lb.)	Ht. (in.)	Normals (1 neighbor)			Signs and Symptoms	Course and Follow up
					Wt. (lb.)	Average for Age Ht. (in.)	Maximum Wt. for Actual Height (lb.)		
G F	13 5	29 7	155 160	62 68 5	89 109	59 61	111 152	Parents concerned about genital development gaining weight rapidly genitalia small erec- tile reflex active, antipruritic and coor- dination poor	After a period of antagonism weight loss, genitalia improved most of height increase took place while no treatment was given (Fig 113 a, b)
H F	15	12 2	205 195	68 3 69 2	101 109	62 61	151 157	Full heavy sluggish with generalized obesity, genitalia appear normal, gets about with diffi- culty, dyspnea and headache, tries hard but has difficulty at schoolwork	Cooperation poor became more active and alert complained less about getting tired all the time Did better work in school
I G	16	15 4	182 131	67 5 67 8	109 121	61 66	145 147	Full heavy, baby faced typical 'fertilized' type, poor work at school female escutcheon gen- italia appear normal, no hair on chest or face	Changed entirely did better work in school, improvement started in about 6 weeks, Began to shave
M H	19	5 2	143 141	67 3 67 5	131 133	67 5 67 8	141 145	Gaining weight rapidly genitalia appear normal, inactive is called 'lazy', no hair on face or chest female escutcheon prestate hardly dis- cernible, is not social	Fat deposits disappeared active and alert, prestate increased in size hair appeared on chest shaving 2 years later—no regression
S B	20	4 4	239 208	68 5 68 5	135 135	68 68	152 152	Generalized obesity with girdle, abdomen mass thigh engorgement large mammary (chief complaint) sluggish and is tired all the time does not get to work on time Genitalia appar- ently normal, headaches	Immediate improvement in general activity and alertness, mammary fat became loose drooping masses later removed by sur- gery warned about diet refused further treatment Gained 10 lb. in next 7 months

natal damage especially when there was no history of disease (to be discussed later) Such a case was M H, Table 2 and Figure 115

TABLE 3
OBESSE THYROIDITIS DEFICIENCY IN THE ADULT MALE

Case	Age	Ht. (in)	Wt. (lb)	Signs and Symptoms	Time Treated (mos)	Loss in Wt. (lb)	Course and Follow-up
M S.	35	63	193	Fatigability, sluggish Precordial pains (EKG negative) Irritability Loss of libido and po- tencia	2	20	All symptoms gone within 2 weeks. Loss of fat deposits out of proportion to weight. Did not return for further treatment or observation
C G	46	67.5	227	Enormously large abdo- men, dyspnea, precor- dial pains fatigability polyphagia polydip- sia (Father of Juve- nile D G) B P 135/100 P 55 B M R -15	3	45	Felt better within one week, lost some weight. On thyroid for 2 mos. and lost 5 lbs. more Wt. 177 P 75 B P 120/76 Follow-up Occasionally nervous but usually care- ful During last year re- mained between 190-200 lbs Feels fine (Fig 111)
B R M D	13	61.5	167	Looks "bloated" slug- gish somnolent P 62 B P 110/80, B M R. -2	2	10	Was apprehensive about taking thyroid took up to 3 grains daily with urging Felt and looked better Discontinued treatment.
	15	61.5	175	Returned 2 1/2 years later Same as above. Con- cerned about sterility B M R -30 B P 105/75	2	25	More active, felt better Up to 4 months after his weight remained at 148 lbs. on 2 to 3 gr desic- cated thyroid
Spermatozoa study (Courtesy of Dr. P. Katzen)							
		Vnl.	Feb 46	Apr 46	May 46	June 46	
		Count	4 cc.	3.3 cc.	3.1 cc.	3.5 cc.	
		Motility	72 million	72.8 M	152 M	140 M	
		Abnormal forms	25%	50%	75%	75%	
			22%	29%	23%	12%	
A R A	42	71.5	193	Out of the Navy 1 yr "Peoples" tired and can sleep all day Can- not carry on work as Engineer Loss of libido head- aches, dizzy depres- sed Duration 8 months. Has been treated with no improvement B M R -30	1 (still being treated)	8	After one week of treat- ment "can work with former efficiency. Is not sleepy anymore. No head- aches. Improvement continued.
L S	45	67	175	Interesting case of "nervous breakdown" treated with sedatives for months for "jit- ters, emotional in- stability, dizzy spells, etc." B M R -11 P 60, Blood chem neg	2	20	In spite of nerves and "tremor, on 2 gr of thy- roid and ant. pit. ext felt better calmer, stronger Went back to active work Did not report for observa- tion for eight months at which time all symptoms had returned. Wt. 155, B M R -23 On desiccated thyroid three weeks with no results On resumption of ant. lobe ext. immedi- ate improvement and re- turn to normal in 1 mo

It was natural to focus our attention on growth in the case of the child of short stature. Response was prompt and regular and repeated measurements were made. The results are recorded in case histories presented later. The charts of growth in Figures 116, 117 and 118 demonstrate conclusively that growth was stimulated and that growth increments were greater by far during periods of treatment than during the intervals. Only after Table 2 was compiled was it found that all patients described therein were above the average in height. Since rapid growth was seldom if ever a complaint, regular measurements and the records thereof were frequently omitted. This omission is thoroughly regrettable because we have obtained conclusive evidence that in the child who was above average in height, growth increment was less during treatment and greater during intervals or after treatment had been discontinued. It is the omission of recorded heights at regular intervals which prevents the construction of a chart to demonstrate this phenomenon.

Our results were consistent, prompt and predictable. Some patients exhibited violent antagonism to diet and treatment. Some of these neurotic individuals refused to give up symptoms and clung to introspection, thus replacing the pathologic condition in explanation of their complaints. In some of these cases results were delayed, occasionally a patient dropped out of sight because of a mood of defeat and discouragement, but many patients, aided by an improved physiology, finally came through, feeling physically fit, mentally alert, and able to meet the stress of modern living.

ILLUSTRATIVE CASES

CASE I—Douglas G., aged 12 years, came to us in 1941 complaining chiefly of "slow" growth, a rapid gain of weight, and tiring easily. He had always been well, an active boy interested in all forms of athletics. His father and mother are obese thyropituitary deficiency cases. The latter is short, the former (Case C G, Table 3) is tall.

Physical Examination Height 53.5 inches, weight 104 pounds (normal 57.1 inches, 78.7 pounds). Appearance short, stocky, and stooped. The genitalia were relatively large (previous treatment for hypogonadal development).

The basal metabolic rate was minus 25 per cent. The roentgenographic findings were negative.

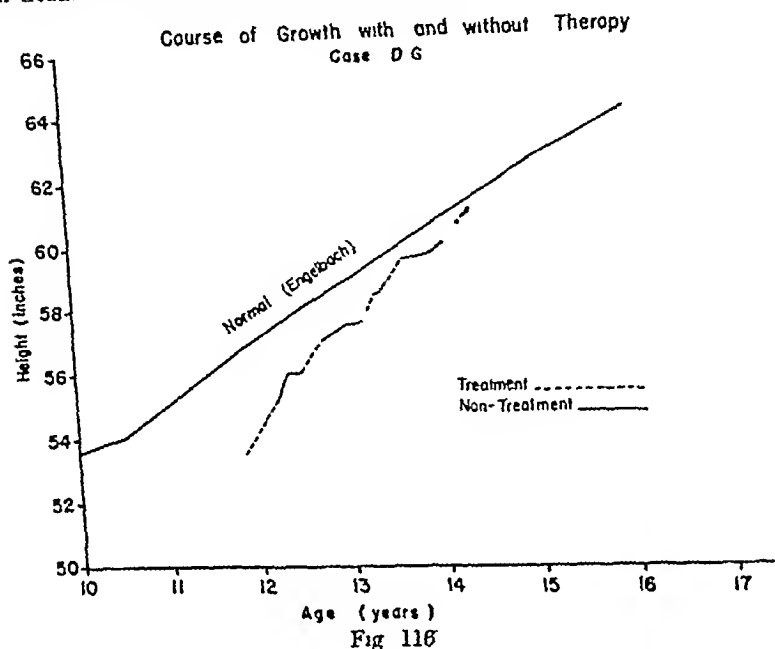
Diagnosis Obese thyropituitary deficiency.

Treatment The previous treatment for genital underdevelopment had not influenced the patient's general condition, growth or weight. Our treatment was begun with desiccated thyroid by mouth and injections of anterior pituitary lobe extract, 1 cc. three times a week, intramuscularly.

Results Within two weeks the boy reported that he "felt better," "lighter," "played ball better," and did not get out of breath as formerly. The general improvement is apparent in Fig. 112 a, b and c, and Fig. 116.

During intervals when no anterior lobe extract was administered, desiccated thyroid therapy was continued. Growth, which had been stimulated, continued

during these intervals for a variable time but at a lesser degree and then ceased. When treatment was resumed growth spurted again.



The patient continued to improve and at the present date (late 1946) his height is 59.6 inches, weight 130 pounds (normal 60.7 inches, 93 pounds)

CASE II—Leonard R, when first seen, in 1941, was a small, chubby youngster 11.5 years of age. His chief complaints were that he was gaining weight rapidly but growing slowly. He had been fairly well all his life with the exception of an enuresis since birth for which he had been treated by others with no alteration in its frequency.

Family History Leonard's father is a slim man, 63 inches tall. His mother is short (55.8 in) and chubby. One sister grew to 62 inches, but in a typical case of obese thyroiditis deficiency (she grew 2 inches under our therapy). She was totally noncooperative and antagonistic. Several cousins on his mother's side were well under 58 inches at full maturity.

Physical Examination Height 52.8 inches, weight 82 pounds (normal 56.2 inches, 75 pounds). There was generalized obesity with exaggeration of the chest, abdomen, girdle and thighs. The genitalia were relatively small and the cremasteric reflex was active. The prepuce was constricted over the midportion of the glans. There were no signs of irritation and there were no subjective symptoms.

The basal metabolic rate was minus 15 per cent.

Röntgenographically the bone age at the wrist was retarded, the sella was small with approximated chnoids.

Diagnosis Obese thyroiditis deficiency, secondary hypogonadism, enuresis on a basis of underdevelopment.

Treatment Desiccated thyroid, 1 to 2 grains daily, and anterior pituitary lobe

extract, 1 cc three times a week, were started and continued for two months. An interval of ten months followed during which the patient was under observation, taking 1 grain of desiccated thyroid daily most of the time. Then because of his shortness of stature (and family history) treatment was resumed with short intervals between courses. This time, treatment continued for four years.

Results During the first two months, the patient's enuresis disappeared entirely. The genitalia improved, the constriction over the gland was no longer evident, and the prepuce normally retracted. After the following ten months of thyroid therapy, it was found that his growth increment was 1.8 inches, relatively normal for his age. His weight rose to 92 pounds, a gain of 9 pounds.

With the resumption of treatment, growth response was immediate without proportional weight gain. Figure 117 illustrates in detail this response to therapy: (a) the spurt of growth with each period of treatment, (b) continuation of growth during first parts of intervals at a lesser rate, (c) cessation of growth, (d) actual growth increment for the first two years, 3.4 inches and 3.1 inches, 1.8 inches is normal average for his age (Engelbach), (e) approach of growth curve to normal.

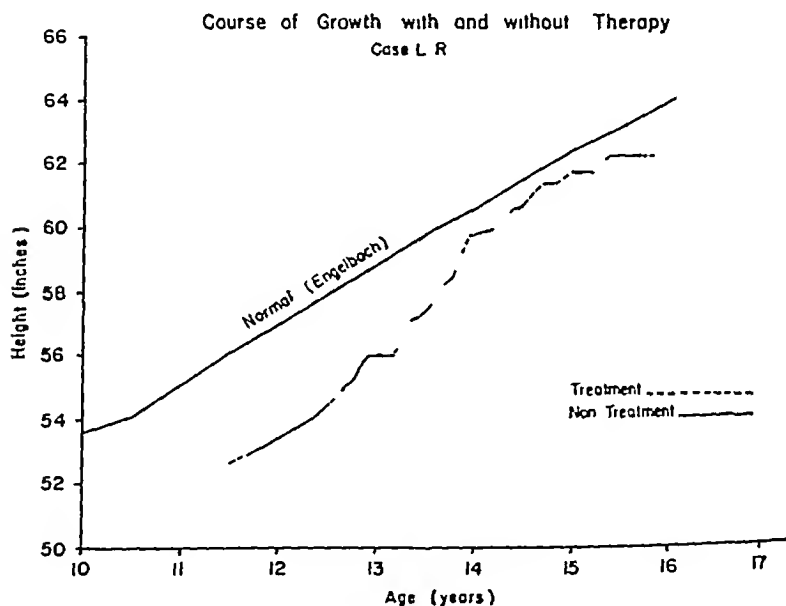


Fig 117

In this case, although bone age was retarded originally and the 13-14 year epiphyses closed late (14-15 years), growth response gradually diminished after 15 years and practically ceased after the patient's 16th birthday. Pubic hair appeared at 13 years of age.

After four years of treatment the patient's height is 62.9 inches, weight 113 pounds (normal 64.7 inches, 114 pounds).

CASE III—Michael D., aged 12, although always tiny, came to us in 1944 with the complaint that he had recently gained a great deal of weight and that he was sluggish and underactive, with underdeveloped genitalia.

Physical Examination. The patient was short, stocky, inactive, and weighed 100 pounds. His height was 54.2 inches (Normal 78.7 pounds, 57.1 inches). The palpebral fissure was small in a round face. There was generalized obesity with exaggeration of fat deposits in the abdomen, girdle and mons. The small

genitalia were buried in the mons fat. The testes were small and the cremasteric reflex was active

The basal metabolic rate was minus 16 per cent The pulse was 70

The roentgenographic study revealed a small sella turcica and a bone age of 9 years

Diagnosis Obese thyroiditis deficiency

Treatment Desiccated thyroid, 1 to 2 grains daily, and anterior pituitary lobe extract, 1 cc three times a week intramuscularly, with intervals of thyroid therapy only, were given

Results This lad's response to therapy was immediate He became more alert and active and the palpebral fissure widened A slight increase in height without actual loss of weight improved his appearance

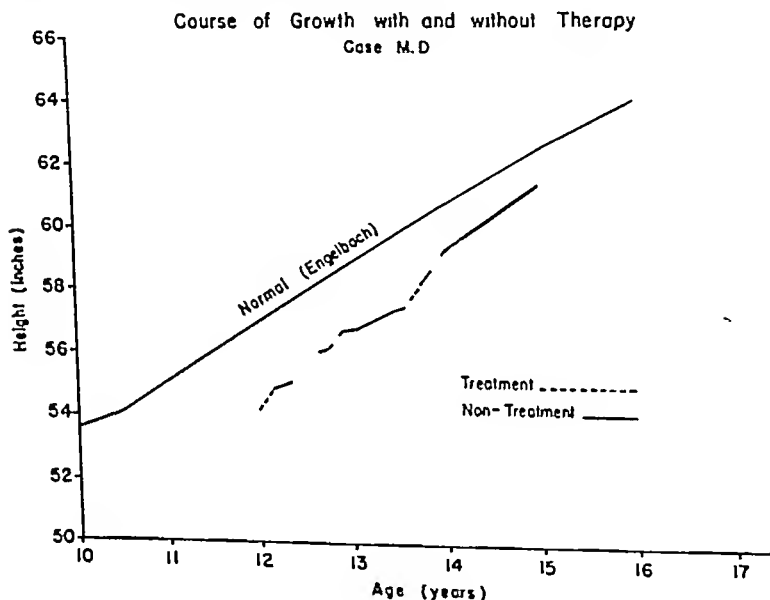


Fig 118

Figure 118 illustrates the results of active therapy. At the age of 15 there was no sign of girdle mons. The patient's height was 59.25 inches, weight 115 pounds (normal 60.7 inches, 93 pounds). Growth increment during each of two years of treatment was 2½ inches, an increase of 0.7 inch over normal. Weight decrease was relative.

COMMENT

In spite of the more obvious manifestations of sexual development in the male, its course in the female from puberty through adolescence to maturity is more easily traced and may be charted with expectancy. This is so, of course, only when all of the secondary sexual characteristics are taken into consideration, i.e., mammae, areola, mamillae, vaginal smears and so forth.

In the young male, no single sign—be it size of genitalia or feminine gentleness—is sufficient to decide normalcy. Whereas the prenatal ovary is relatively safe in utero, the testes in utero are subject to re-

gressive phenomena of development during the last two months of gestation.² For instance, the testis of the 32 weeks old male fetus is fairly well developed, the tubules are well convoluted, what were solid cords of cells now have clear lumina and the cells in the intertubular spaces are crowded. At this point, however, the testis regresses gradually so that at birth (40 weeks) it resembles histologically its former 24 weeks' state of development: the tubules are no longer uniform, their lumina are not detected, the intertubular spaces dominate the picture. After birth, the testis does not reach its thirty-second week's maximum degree of intrauterine development for seven months to one and a half years.

This regression in the development of the testes is due undoubtedly to maternal estrogens. The presence of estrogen in the body of the newborn female has been known for a long time. The latest corroboration was the discovery of highly cornified estrogenic smears in the vagina of the female newborn.³ It has also been shown that the urine of the newborn male (as well as the female), when injected into immature male mice produces hyperemia and hemorrhage in the testes, the prostate and seminal vesicles, but increases the size of the mammary and the uterus masculinus.⁴ These observations merit further investigation and their import demands more care in the therapeutic administration of estrogens to the pregnant woman in the latter months of pregnancy, lest the testes of the male fetus be additionally retarded in their maturation.

In the young and also in older males, evidence of prenatal damage of testes is not uncommon. Complete destruction produces the typical eunuchoid male. Partial damage may produce variable types of retarded development for which, to produce a relative normal state, additional gonadotropins may be needed.

In the case of dystrophia adiposogenitalis and its many types, though hypogonadism exists as a single sign in a complex syndrome of hypopituitarism, prenatal effects may add difficulties. The gonads have no independent activity,⁵ they are dormant when the pituitary fails, they are deficient when the pituitary is inadequate. Whether dormant or deficient, these gonads cause signs and symptoms sufficient to dominate the picture and become the sole target of therapeutic aim. No mere substitution of gonadal hormones will alter the state of the gonads, nor will it alter the chain of deficiencies caused by hypopituitarism. Thus, the degree of underfunctioning of the pituitary glands, plus the unknown quantity of retardation due to possible prenatal effects, influence the degree and rapidity of response to therapy. No changes caused by gonadotropic stimulation (even if an efficient gonadotropic hormone were available) could alter the metabolic deficiencies, and no growth hormone (even if the available ones were efficient in the human) could alter all phases of the complaints met in hypopituitarism.

Medical literature abounds with controversial data concerning the development to be expected in the obese child, the underdeveloped child with delayed maturity, and the dwarfed child. The status of adiposogenital dystrophy as a clinical entity is questionable. Migratory or undescended testes may or may not correct themselves at puberty, obesity may be endogenous or exogenous and children may "grow out" of it as they get older.⁶ Yet it must be admitted that many adults are seen not only with a "Frohlich" type of physique but with progressive signs of pituitary deficiency. It must also be admitted that the underweight child can no more gain weight by eating ravenously than the fat one can control the feeling of hunger produced by the absence of the autonomic feeling of satiation after eating.⁷ The experiences of many attest to the fact that disappointment sometimes awaits those who depend upon puberty to effect a correction. The cases herein described, and many others, definitely demonstrate that the older the patient, the more difficult it is to attain and maintain a relatively normal state. Besides, the more severe the obesity, the more difficult it is to control or reduce. The results herein described are neither novel nor original. The earlier the treatment, the more rapid and permanent are the results.^{8,9}

The term "obese thyroid-pituitary deficiency" isolates a group of cases, of *pituitarism* from many other varieties, especially the nonobese types which do not respond to therapy with predictable uniformity. Its obesity may be slight, its genital involvement may be difficult to evaluate, its associated signs of hypopituitarism may be masked by degree, by temperament and/or by compensatory mechanisms. Variability in signs and symptoms must be expected. The character of the syndrome depends upon (1) age of onset, which may be hard to determine, (2) severity or degree of deficiency, also difficult to evaluate, and (3) susceptibility of organs affected. The wide diversity of the symptoms must not obscure the diagnosis lest treatment become symptomatic.

Our clinical experiences demonstrate a prompt response to therapy in *all* phases of the complaint—and this distinguishes the syndrome. This response has seemed to follow along lines of normalization of physiological processes toward a balanced synchrony of statural growth, sexual development, and mental attainment. Such synchrony constitutes obvious phenomena in the relatively normal. Thus, in our cases we have seen the phenomenon of lessened growth produced by the treatment of boys originally above average in height, and increased growth in relatively dwarfed children produced by the same treatment.

All physiological phenomena, and especially those which took place in our experience, point to the fact that many synergists and antagonists lie between a desired result and the reagent administered to bring it about. We realized very early that no isolated physiological effect could be attained without *these potential interrelating effects*,

American Diabetes Association and consisted of scientific papers relating to clinical diabetes and carbohydrate metabolism I think it can be said that never again will it be possible to bring together a group of men so fully representative of a single field of medicine and science All the proceedings of the Sixth Annual Meeting will be published in Volume 6 of the *Proceedings of the American Diabetes Association*

This Association has published annually the *Proceedings of the American Diabetes Association* which consists of its business activities as well as its scientific programs It is also responsible for the distribution of *Diabetes Abstracts*, quarterly and is of invaluable assistance to the members of the Association in keeping current with the literature relating to the subject The publication of *Diabetes Abstracts* has been made possible by the great generosity of the Eli Lilly Company The Association has complete control of its mailing list

During the commemorative and scientific sessions in Toronto, the Council of the American Diabetes Association considered and acted upon many important subjects important to the physician and the patient Committees of the Association were created to study the question of the establishment of a lay journal Further Committees were established to study the foundation of local diabetes associations, and a committee was established to study the question of vascular complications which would work jointly with the American Heart Association In addition there are various committees such as the Committee on Statistical Investigation and a Committee on Nostriums These committees have been at work and their results have been published in preceding issues of the *Proceedings* The medical profession is greatly indebted to the activities of these committees Important is the work of the Committee on Insulin Mixtures and Insulin Syringes Attempts will be made to suggest a standard insulin syringe and also to cooperate with the manufacturers of insulin in the production of the various and most advantageous types of insulin It must be obvious that all of these activities will yield even greater profits than have existed, and that continued activity can only accrue to the benefit of the diabetic

It is not necessary to list many of the dramatic changes that have taken place since the discovery of insulin Too many physicians can recall the pathetic state of the juvenile diabetic in the preinsulin era, when life expectancy was at a maximum of two to three years Then, too, who has forgotten the completely invalided severe diabetic who was kept alive to "die from starvation" Diabetic coma almost invari-

Quite a few of our typical patients with adiposogenital dystrophy appeared with genitalia already overstimulated by chorionic gonadotropins or testosterone (Fig 112) We are not ready to admit that the penis, buried in mons fat and even accompanied by "small" testes, deserves special therapeutic consideration unless it can be demonstrated that we are dealing with a physiological castrate We look with disfavor upon the therapeutic production of rapid growth in the dwarfed juvenile, when that growth is accompanied by overstimulation of the genital organ, we also deplore the stimulation of rapid growth in youngsters, when that growth is accompanied by overproduction of "fat" or somatic underdevelopment (underweight for height) And lastly, we question the potentialities in a long, flaccid therapeutically stimulated penis We question all developmental phenomena unless there is synchrony in body growth, sexual and mental development To attempt to alter any one phase of this synchrony, when all are at fault, is to shift the unbalance

In our experience there has been no evidence of any untoward effect from the administration of anterior lobe extract Administration in 90 per cent of our cases has been by the parenteral route Beck¹⁰ says, "My personal experience with the oral administration of pituitary extract does not permit me to doubt results However, they are not comparable with those obtained by the injection methods" In the same article, Beck says further, "I call attention to the fact that the effect of anterior pituitary lobe extract was augmented by the addition of thyroid This view has been confirmed by Timme, Hoskins, Tierney, Englebach, McMahon, Osborne, Schaefer and many others" To this list we may now add Cushing, Jacobsen and Cramer, and Goldzieher¹ As for the general results with anterior pituitary extract, we cannot deny the clinical findings and experiences of Englebach, Beck, Cushing, Pardee, Timme, Calder, Rowe and Lawrence, Jacobsen and Cramer, Goldzieher, and many others¹

CONCLUSION

1 Obese thyropituitary deficiency is a distinct clinical entity in spite of the variabilities which exist in the individual cases

2 The crude water-soluble extract of the anterior lobe of the pituitary gland in conjunction with desiccated thyroid and sensible eating produces prompt, uniform and predictable results in all phases of the complaint

3 The results are evidenced in a return to normal, well balanced, and coordinated physiological processes

4 No untoward effects were encountered

5 Prenatal effects on the male gonad must be considered as a possible etiologic factor in hypogonadism (underdevelopment) in addition to an underfunctioning pituitary (pituitary inadequacy)

6 The diagnosis of endocrine unbalance depends on symptoms and signs as they are associated and not on the individual signs, no matter how obvious

7 An endocrine effector cannot always produce an expected or desired result because of the many intervening synergists and antagonists which exist between its administration and the receptor

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SOME COMMON OPHTHALMOLOGIC PROBLEMS IN PEDIATRICS

BENJAMIN ESTERMAN, M D °

THE general practitioner and the pediatrician are usually the first to come in contact with the majority of eye disorders in children. In some, the extent of cure often depends upon the promptness with which the disorders are recognized and treatment instituted. Outstanding among these are three conditions in which the family doctor can be of particular service, namely (1) strabismus, (2) congenital dacryostenosis, and (3) congenital cataract, and these will be discussed first. Subsequently the general features of other ocular diseases commonly met in childhood will be taken up more briefly.

STRABISMUS

Unfortunately, even in present day practice, the emphasis here is on appearance rather than on function. Too often the patient is brought to the ophthalmologist with strabismus of several years' duration and the story that the parent had been advised to "wait until the child is older." This child, more often than not, reveals a well developed amblyopia exanopsia (poor vision resulting from disuse of the squinting eye) and the older he is the less likelihood there remains of restoring useful sight.

Pathology.—To understand the problem of amblyopia better, a few words about strabismus in general may be in order. Eliminating the less common forms which are of more interest to the ophthalmologist than to the general practitioner, strabismus is mostly of two varieties: tropia, i e., a frankly and consistently deviated eye, and phoria, i e., an eye which has a *tendency* to deviate, controlled at least part of the time, consciously or not, by the patient, but becoming manifest under stress, fatigue, tantrums, illness or excessive ocular effort. Thus we may have

Esotropia	frank convergent strabismus
Exotropia	frank divergent strabismus
Esophoria	a tendency to converge
Exophoria	a tendency to diverge

Some strabismus may be of one eye only, for example, right esotropia in which the right eye is consistently the squinting eye. Others may

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be of the alternating type where, in a given patient, strabismus is exhibited sometimes by the right eye, sometimes by the left, e g., alternating esotropia or alternating exotropia

Children with convergent strabismus are usually farsighted, those with divergent strabismus nearsighted. Often in the young child, correction of the refractive error alone may eliminate a phoria or even a tropia

Now where an eye is strabismic, its continued use in conjunction with the straight eye would result in double vision—one of the most uncomfortable symptoms known to medicine. To avoid this, the child unconsciously *suppresses* the function of the squinting eye. If this is done only occasionally (phoria) the vision in this eye may remain good or even normal. But where this condition is constant (tropia) and always in the same eye, the vision usually fails to develop. This is known as *amblyopia*. The exception is in alternating tropia, in which either eye will deviate, and here logically enough no amblyopia develops since each eye has an opportunity to be used.

At what age does this process begin? While estimates vary, as do children, it is safe to consider that binocular vision is usually well established before the age of 1, and it is generally thought that many cases of amblyopia cannot be improved when treatment starts after the age of 6. Occasionally the onset of strabismus is noted at about the age of 4, but these probably have been cases of latent strabismus (phoria) which become frank squint (tropia) by dint of increased use at close range (picture books) illness (measles, pertussis) or a violent fall, so that parents will often date the strabismus from these events.

Treatment.—At what age should treatment begin? Since the object of our treatment is first and foremost the prevention of amblyopia, and since a frank tropia which consistently involves the same eye may be considered an excellent candidate for amblyopia, treatment should be instituted as soon as the diagnosis is established. The child must first be refracted under atropine or scopolamine cycloplegia and if the refractive correction is sufficient to be effective, glasses should be worn constantly for a trial period of at least a few months. Small children may be given frames which tie behind the head with tape and lenses may be shatterproof for greater safety. If the eyes are straightened by glasses, they should continue to be worn, and gradually reduced in strength if in so doing the squint is not restored. Sometimes such children, when older, can forego the constant wearing of glasses if the binocular function has become well developed.

If, despite glasses, the squint persists, it becomes necessary (1) to stimulate the amblyopic eye by occluding the fixing eye, (2) to straighten the eyes so that they may have the opportunity to coordinate and achieve binocular vision—thus by orthoptic exercise or surgery or both. The latter are of course beyond the scope of this article.

since they must of necessity be handled entirely by the specialist. Some words may be permissible, however, on the optimum age for surgery, since there seems to be a general belief that children should be adolescent before surgery is undertaken.

In cases of frank and consistent strabismus, which have shown little improvement with glasses or orthoptic exercises, operation may quite properly be undertaken at age 3 or 4, and should certainly have been done by age 6, first because the subsequent development of binocular function is easier the younger the child, and second because experience with many such children has shown that by the age of 5 or 6 there is definite psychologic trauma due to a consciousness of deformity. The child under 4 is relatively little exposed to the critical scrutiny of other children, and if the parents are intelligent they have avoided drawing his attention to his own deformity. (Incidentally the physician must never discuss this with the parents in the child's presence.) The child over 5 characteristically shows signs of conscious or unconscious embarrassment, ranging all the way from scowling or ducking the head to excessive shyness or a compensatory over-belligerency.

Tests for Detection of Strabismus.—The general practitioner and the pediatrician can and should learn a simple test for the detection of strabismus, since the deformity is not sufficient in all cases to permit diagnosis by simple inspection, and particularly since even a barely discernible squint may lead to a profound amblyopia. Conversely, he may, by the same means, determine the *absence* of strabismus in the frequent cases in which an overanxious parent has wrongly made the diagnosis on the basis of a wide epicanthal fold so common in the young.

The child, in the parent's lap, and the physician are seated face to face about 2 feet apart. A small light is used, usually that of an ophthalmoscope (children often fear the pocket light from association with the throat examination, a small red or green light is even better because it is still more unlike that used in the throat or ear examination). The physician holds the light in one hand a few inches before his own face and about 15 inches from the child's face so that the child in watching the light might just as well be looking at the physician's eye beyond it. This light is held motionless throughout the test. The doctor is thus in a position to see which eye is apparently fixed on the light and which is deviated. The next moment, he places a small card to cover the fixing eye, *at the same time* carefully observing the apparently deviating eye. If the latter does not then swing into position so that it becomes fixed on the light, it has probably been straight all along and the strabismus is only an illusion. But if the deviating eye has been *crossed* prior to the covering of the straight eye (Fig. 119), it will then be seen to swing outward from its crossed

position to that which will bring it to look directly at the light, if the eye has been *divergent* it will come into line by turning medially in order to look directly at the light (Fig 120) Given a cooperative child, even aged 2, this test can be done in 15 seconds

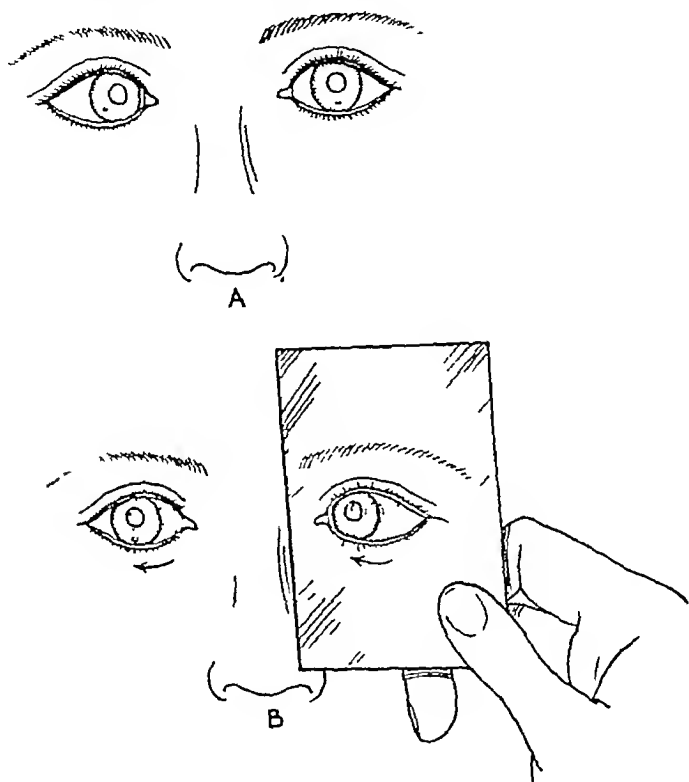


Fig 119—Right esotropia. A, The child is seated facing the examiner, with a lighted ophthalmoscope bulb held about 15 inches before the child's eyes. The minute reflection of this light may be seen in the lower portion of each cornea. The left is the fixing eye and looks directly at the light, the right is convergent.

B, Now, while carefully watching the convergent eye for shift, an opaque card (here drawn as though transparent for the purpose of illustration) is held before the straight left eye, blocking its fixation. At this instant, the convergent eye is seen to shift laterally (arrow) to the fixing position. It is this lateral shift to the fixing position which makes the diagnosis of esotropia.

A marked esotropia will show a marked shift as in the case illustrated. In a slight esotropia the shift may be only 2 or 3 mm.

If the squinting eye is already amblyopic, the child may resist the covering of the good eye by attempting to brush the card away with his hand, or by moving his head to get out from behind the card—

simply because he resents being prevented from using the good eye. Or, if amblyopic, the crossed eye may wander in attempts to focus on the light.

All of the foregoing will determine the presence or absence of tropia. With a little practice, this simple test may also be used to detect phoria (Fig 121). The same procedure is followed but now the atten-

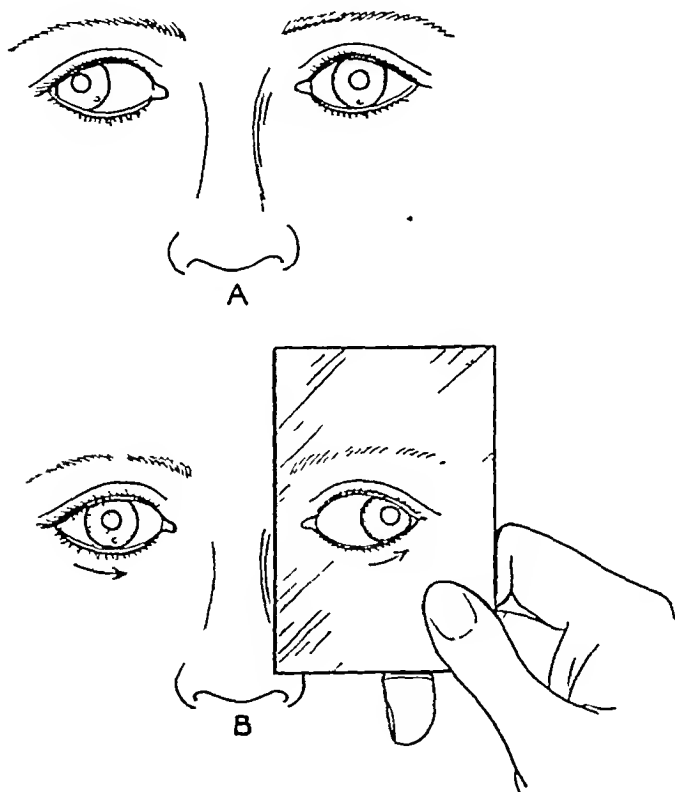


Fig 120—Right exotropia. Here (A) the right eye is divergent, while the left fixes the light.

When the fixing left eye is blocked (B) the divergent right eye swings medially (arrow) to fix upon the light. It is the medial swing of the eye the instant it is called upon to fix that makes the diagnosis of exotropia.

tion is focused on the eye behind the card. Since phoria is only a tendency to deviate, both eyes fix upon the light until the interposed card, by blocking one eye and so destroying the binocular coordination, allows that tendency to become manifest. Thus the apparently straight eye will deviate only when blocked.

Occasionally strabismus may be elicited only if the same test is

performed with the child viewing a light 15 or 20 feet distant instead of at 18 inches. For this it is often advisable to have the nurse or parent hold the flashlight at the opposite end of the room and cause it to flicker, thus better attracting the child's attention. Sometimes cases of tropia for a near light become phoria for a distant one or vice versa.

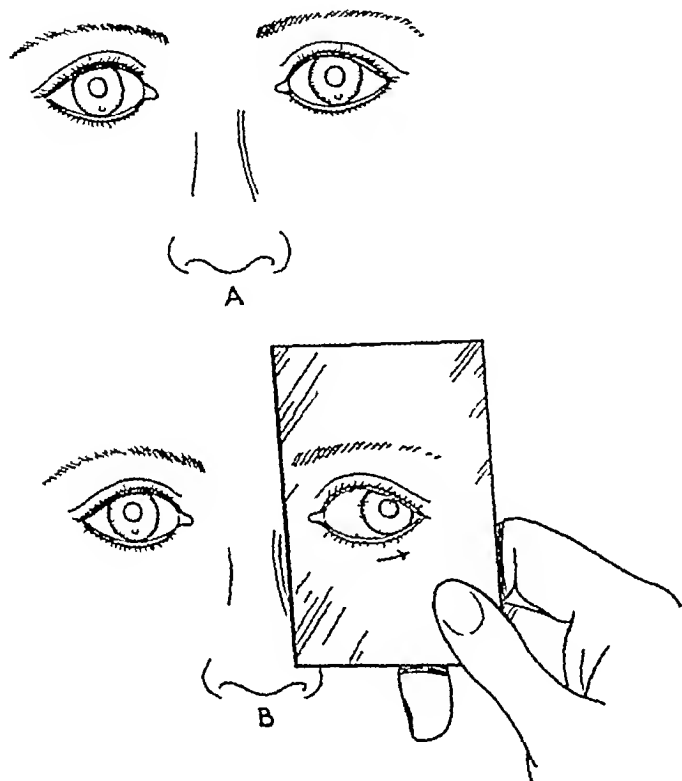


Fig 121—Left exophoria. Although the left eye has a tendency to diverge, the child is able to keep it in position by making an effort. Thus, in A, both eyes are straight and fixed upon the light. In B, this effort has been interfered with by blocking the eye, causing it to diverge. (The card is opaque, but is drawn as though transparent for the purpose of illustration.)

When the card is removed, the left eye may be detected in the process of returning to the fixing position, shown in A.

It is again emphasized that with a little practice, all of the above testing can be performed in less than two minutes.

In addition, in children over 3 or 4, it is possible for the examiner to reassure himself of the absence of amblyopia by checking the visual acuity of each eye separately. Many physicians do not perform this

test because of the child's ignorance of the alphabet used in ordinary Snellen eye charts. In fact, a visual defect often remains undiscovered until the child is tested in school, with the teacher instead of the doctor performing a part of the child's physical examination (for such it is, just as surely as is the determination of the blood pressure or the auscultation of the chest).

Any surgical house can supply Snellen eye charts designed for pediatric use. The most common are those with familiar pictures, and those with the letter E turned in different directions, the latter type is preferable, in my experience. On one visit, the E chart is shown to the child and mother and its purpose explained. The mother is then given or instructed to make a round card about 4 inches in diameter with a single letter E on it about 2 inches in height and advised to use it as a game at home, with the child holding the outstretched fingers of his hand to correspond with the directions of the "fingers" on the letter E. The position of the latter is changed from moment to moment by the mother holding the card, and the child learns to respond accordingly. Thus, trained, it takes no more than a few minutes during his second visit to the doctor to demonstrate the acuity, or lack of it, in each eye.

Where substantial refractive error or ophthalmoscopic evidence of pathologic change have been ruled out, markedly diminished acuity in a consistently squinting eye must be considered presumptive evidence of amblyopia. Occlusion of the good eye by means of a snug patch may be started as early as age 2. Often two or three hours a day is sufficient, while in cases of profound amblyopia, I have not hesitated to patch the fixing eye all day every day for four to six weeks at a time, with rest periods of several weeks between courses. The parent should be warned to expect, and indeed to hope, that the formerly straight eye may be the one to become crossed, and to recognize that the purpose of this treatment is not to straighten the eyes, but to correct the poor vision.

The period concurrent with or shortly following courses of occlusion is often ideal for starting orthoptic training in suitable cases. In fact there are on the market inexpensive sets consisting of stereoscope and appropriate slides which may be used at home by an intelligent parent and cooperative child under the supervision of the ophthalmologist as an adjunct to other treatment or pre- and postoperatively.

Where the strabismus is of the alternating type from the outset and particularly where visual acuity is equal in the two eyes or almost so, occlusion is usually unnecessary. Where the strabismus is only occasional (phoria) and acuity is equal, occlusion is definitely contraindicated, this is logical since even without interference the child is struggling to maintain binocular vision and occlusion of course makes binocular vision impossible.

What the General Practitioner or Pediatrician Can Do.—Thus the general practitioner or pediatrician is in a position to make a real contribution to the management of strabismus by the following

- 1 Recognition of the condition and of the importance of early treatment
- 2 Awareness that prevention of amblyopia is more important in the child of 2 to 5 than the cosmetic deformity
- 3 Awareness that the cosmetic deformity becomes a psychological problem beyond the age of 5, and should be corrected by then
- 4 Ability to make a simple test for strabismus, to determine
 - (a) If the strabismus is only apparent and not real, or
 - (b) If the case is only a phoria, or
 - (c) If the case is a tropia and if so whether the child suppresses one eye entirely as shown by the test and by markedly diminished acuity (amblyopia)
- 5 In the latter event, the practitioner may quite properly institute occlusion of the fixing eye even before the child is seen by the ophthalmologist, especially in such localities where the latter is not readily accessible
- 6 Making it a practice in all cases, strabismus or not, to test visual acuity as an integral part of the complete physical examination

CONGENITAL DACRYOSTENOSIS

This is not a stenosis in the true sense, but an obstruction of the nasolacrimal duct either by a mucus plug or an imperforate lower end of the lacrimal sac. Its importance to the general practitioner lies in the fact that he can cure the majority of cases himself.

The first symptom is usually tearing of one eye, rarely both eyes, and this becomes manifest during the first few weeks of life. Discharge, mucoid or purulent, comes *later* and is the result of stasis of the tear fluid causing secondary infection. This provides an important differentiation from ophthalmia neonatorum, which is purulent from onset and usually occurs within the first week, while the mucoid discharge and hyperemia of the conjunctiva resulting from silver nitrate clear up a few days after birth and are rarely accompanied by tearing. A drop of fluorescein 2 per cent solution should be instilled to make certain that the tearing is not due to a corneal abrasion.

Another symptom, though less common, is a swelling in the region of the tear sac—the area just inferior to the inner canthus. The parent should look on while the doctor expresses pus from the punctum into the conjunctival sac by making gentle but firm pressure over this area. The parent is then told that the treatment at home consists of not thus emptying the sac so that it regurgitates into the eye, but of making pressure with the finger tip backward and downward thus

ably meant death, and surgery in the diabetic was a battle between the surgeon and the internist. Today, we see juvenile diabetics growing into adulthood as "normal" citizens who accept all of the responsibilities thrust upon them. Pregnancy in the diabetic is no longer prohibited and the mortality of the offspring is not too high to allow diabetic mothers to carry on. Life expectancy of the diabetic now approaches seventy years, only slightly short of normal expectancy. Even bolder advances are being made. Diabetics are now candidates for insurance which heretofore has been completely denied them.

All of these are tremendous advances of comparatively rapid speed, but in spite of this greater challenges are before us. The degenerative processes which are disproportionately high in the middle-aged and elderly diabetic force us to concentrate our researches on the all too common complications such as retinopathy, coronary disease, renal complications and peripheral vascular disturbances. It may be that these are not the complications of diabetes, but in an individual who has diabetes there may be a fundamental disturbance and diabetes may be only a single expression of this fundamental disturbance.

The past twenty-five years have brought tremendous aids to the physician in the care of his diabetic patient. However, with the newer studies of the intermediary carbohydrate metabolism, isotopes and alloxan, the diabetic may expect even greater advances in the next twenty-five years than he experienced in the past. This challenge is being accepted by the individual physician as well as by the American Diabetes Association and the philosophy of the Association as well as the activity of its various committees is predicated on the belief that by persistent and unrelenting effort the diabetic can be assured of even greater rewards.

"milking" the contents down through the nasolacrimal duct and into the nose. This should be done once or twice daily, when enough mucus has accumulated in the sac. Its repeated forced passage down the duct often is in itself sufficient to clear out any mucus plug. In addition, two drops of a mildly astringent and vasoconstricting solution, such as the following, should be instilled in the eye at every feeding time.

Zinc Sulphate	0 02
Boric Acid	0 20
Epinephrine 1 1000	1 0
Distilled water	10 0

If this procedure is not successful, the tear sac should be irrigated by an ophthalmologist, and this is best done before the child is 2 or 3 months old. The reasons for promptness are twofold: (1) the secondary infection is less likely to have caused permanent changes in the duct and (2) prior to 3 months irrigation usually can be done without general anesthesia. My method has been to have the child and its nursing bottle brought to the office at feeding time, to wait about thirty minutes beyond this time in order to allow it to become too hungry to pay attention to anything being done to it when the nipple is finally placed in its mouth. A drop of 0.5 per cent pontocaine is instilled to diminish the wink reflex, the punctum is gently dilated with a conical dilator, and normal saline is gently forced into the sac with a fine, blunt canaliculus needle. Often the child will seem to gulp or gag when the fluid passes into his nasopharynx. The saline may be colored green with a drop of fluorescein to make it more easily detected in the nose.

If the passageway cannot thus be opened after one or several attempts it then becomes necessary to use lacrimal sounds to establish patency, and this is usually done under light general anesthesia.

CONGENITAL CATARACT

The physician who recognizes this condition very early renders a valuable service to the child, because it is being realized more and more that macular function develops best during the first year, and probably during the first six months of life. Unless other signs make the ophthalmic surgeon suspicious that there is additional pathologic aberration in the globes (in which case operation is dangerous), surgery should not be delayed. Fortunately the procedure is simple and takes less time to perform than to describe. Under light general anesthesia a fine knife-needle is passed obliquely through the cornea to make several incisions in the anterior capsule of the cataractous lens, the soft lens matter then absorbs after a few weeks' contact with the aqueous, leaving a clear pupil.

Every newborn infant should, during the first few weeks of life and again at 6 months, be examined for lenticular opacities. This is easily done in a darkened room (so that the pupils will not be too contracted) using a well focused ophthalmoscope. The examiner looks through the "zero" lens, holding the instrument about 10 inches from the baby's eye, again the latter will be much more docile if he is taking his bottle at the time. A uniform red fundus reflex throughout the entire pupillary area is reasonable assurance that the lens is clear. The examiner may then move closer to the pupil to do a routine inspection of the fundus. If, in the first instance, any portion of the red reflex is darkened by a shadow, or if the pupil remains too small for a satisfactory view, one should not hesitate to instil two drops of pare-drine 1 per cent or homatropine 1 per cent one-half hour before examination. This should also be done routinely if there is any history of other cataracts in the family or of rubella in the mother during the early months of pregnancy, since this is a common cause of congenital cataract.

OPHTHALMIA NEONATORUM

This condition is too well known to be discussed in great detail. In recent years the sulfonamide drugs and penicillin have been the therapy of choice. Of the former, sulfathiazole and sulfapyridine have been the most widely used, oral dosage being 0.25 gm initially, followed by 0.125 gm every four hours for four or five days, or at least until one day after discharge has ceased and smears are negative.

Even more dramatic are the results obtained from intramuscular injections of 5,000 units of penicillin every three hours, with or without instillation of three drops of penicillin solution, 500 units per cubic centimeter, in each eye every three hours. By this method, smears are usually negative in one day, discharge clears by the second or third day, and recovery is complete in four to six days.

It is still important while there is much discharge to keep the conjunctival sac free of pus by normal saline irrigations every hour or two. However, care should be exercised in administration of this treatment lest too much enthusiasm cause injury to the corneal epithelium resulting in ulceration and scarring.

INTERSTITIAL KERATITIS

This is a prolonged and disabling disease, fraught with the danger of permanent visual impairment. It is characterized by pain and lacrimation, with photophobia usually marked, and identified by a haziness of the deeper layers of the cornea, at first detected only by magnification or with the slit-lamp, in some cases becoming so marked as to make the entire central portion of the cornea a light gray. The redness of the eye is of the ciliary type—the engorged vessels radiating from

the limbus like a sunburst—rather than the diffuse and more uniform injection of conjunctivitis

Its etiology is predominantly congenital syphilis (although tuberculosis, nephritis, smallpox and malaria have been implicated in rare cases) and the familiar triad of prominent frontal bones, saddle nose and Hutchinson teeth help materially in pointing to the diagnosis. It is rare in children under eight and is more common in girls than in boys. It often involves one eye weeks or even months before the other. Treatment consists of antiluetics, mydriatics, heat, artificial fever, intravenous typhoid injections, foreign proteins and dark glasses. Its duration may be many months, subsiding by lysis and leaving cloudy corneae and diminished vision. Recent experience with adjuvant therapy in the form of several million units of penicillin over a period of a few weeks hold some hope of lessening duration and severity, but more investigation remains to be done along this line.

It should be kept in mind that true congenital lues is not passed on to the third generation, and much needless turmoil in the family may be avoided by not discussing the etiology save where some direct benefit will accrue.

PHLYCTENULAR KERATITIS

The corneal form of this disease is less common but more severe and may be more permanently disabling than its conjunctival counterpart. It is characterized by single, minute, discrete, superficial infiltrates of the cornea of one eye, accompanied by intense pain, lacrimation, photophobia and spasm of the lids. This infiltrate very quickly becomes slightly elevated and presents the appearance of a tiny nodule, about 1 mm. in diameter which does not stain with fluorescein and is surrounded by clear cornea. After a few days, the corneal epithelium at the apex of this nodule becomes eroded and will then take the fluorescein stain. Shortly after this the symptoms begin to subside, but a tiny vascularized scar remains. Often the process is repeated in other parts of the cornea and if the child is so unfortunate as to have had one or more in the pupillary area, a permanent visual defect results.

The same process in the bulbar conjunctiva presents symptoms very much milder and, of course, with no impairment of vision.

For the corneal phlyctenule, a drop of cocaine 3 per cent may be required before the child will permit examination. Local treatment consists of atropine sulfate 0.5 per cent solution or scopolamine 0.25 per cent solution instilled twice daily and mercury in the form of yellow oxide 1 per cent ointment or calomel powder dusted on to the cornea and bulbar conjunctiva three or four times daily. Dark glasses may relieve the photophobia.

More important is the general treatment, since this condition is most commonly found in children who are somewhat subnormal physically.

Anemia, malnutrition, foci of infection and errors in hygiene should be corrected. Diet should be low in carbohydrates and high in proteins. The occasional very stubborn case may be controlled more readily by foreign protein injections. Many cases seen in eye clinics with strongly positive Mantoux tests but no active tuberculosis have apparently been helped by courses of tuberculin injections.

Points of similarity between interstitial and phlyctenular keratitis include (1) involvement of cornea, with resultant opacification and vascularization, (2) photophobia usually marked, pain and lacrimation often present, (3) ciliary type of injection, rather than conjunctival type, and (4) absence of discharge so common to conjunctivitis.

The principal *differential points* between interstitial and phlyctenular keratitis are

<i>Interstitial Keratitis</i>	<i>Phlyctenular Keratitis</i>
1 Diffuse involvement of considerable area of cornea, especially center	1 Single minute, discrete nodules anywhere on cornea.
2 Infiltrate is in deep layers of cornea	2 Infiltrates are superficial and cause tiny elevations of epithelium
3 Never stains with fluorescein.	3 Apex of phlyctenule stains with fluorescein after first few days
4 Duration many weeks or months with little remission until attack subsides	4 Duration of single attack rarely more than one week, but may be many recurrences in fresh areas of same cornea
5 Stigmata of congenital lues present.	5 Stigmata absent.
6 Wassermann test positive	6 Wassermann test negative

VERNAL CATARRH

Here the prominent symptoms are itching and burning, sometimes intractable, tearing and photophobia are less pronounced, pain and blepharospasm usually absent. Discharge is scant, stringy, mucoid in character. All cases are bilateral and recur annually for from two to ten years coinciding with warm, humid weather.

Objectively, the everted tarsal conjunctivae appear to be covered with a mosaic of pinkish gray, flat-topped papules, over which is spread a bluish white, stringy secretion, so that the picture has often been described as resembling cobblestone pavement over which milk has been spilt. In some cases, papillae may be seen at the limbus of the cornea, as well. Stained smears of the secretion usually show large numbers of eosinophils.

The disease is characteristically resistant to treatment, and since annual migration to places with cool, dry climate is rarely feasible, palliative measures are in order. These consist of dark glasses, cold applications, ephedrine or neosynephrin drops. Cold boracic acid lavage is often used, but I have found the following solution very effective in reducing discomfort.

Monohydrated Sodium Carbonate
Distilled water

10
100.0

This should be kept in the refrigerator and used ice-cold as an eye bath every few hours

Radium and carbon dioxide snow have been employed in the more severe cases, not without an element of danger. Very recently, the successful use of radiation with the safer beta rays has been reported and this may well become the therapy of choice.

FOREIGN BODIES AND INJURIES

The removal of embedded corneal foreign body in the child presents the problem of avoiding general anesthesia. It should be remembered that the doctor who instills the anesthetic eye drops will be mistrusted by the frightened little patient, resulting in a struggle and much lacerated corneal epithelium. My method has been to seat the mother and child in the waiting room and have the mother instil drops of

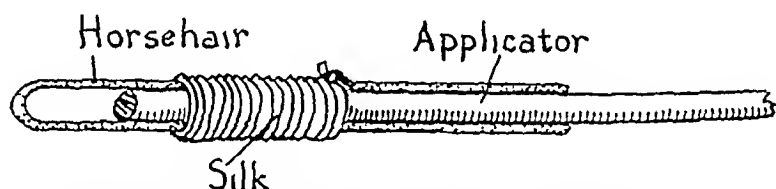


Fig. 122.—Horsehair loop for removal of superficial foreign bodies of cornea (magnified 2 ×). The loop should extend $\frac{3}{4}$ inch beyond applicator.

pontocaine 0.5 per cent or butyn 2 per cent every few minutes for five doses. On return to the dark room the foreign body is removed from the anesthetized cornea while the child believes himself to be undergoing merely another examination.

For the general practitioner, the ideal instrument for corneal foreign bodies is made of a minute loop of horsehair, tied to the end of a wooden applicator or toothpick by means of silk (Fig. 122). This is safer than the needle or spud and yet much more precise than the usual cotton-wrapped applicator which so often abrades much of the corneal epithelium while removing the particle.

At this point, I wish to make a plea for the more general use of condensed illumination and of fluorescein in the examination of the anterior segment of the eye. An ordinary 25 watt incandescent light a few feet away from the eye, focused to a sharp point by means of a convex lens (a simple "burning glass" such as used by children to ignite wood or paper), will disclose more detail of cornea and iris than will a much more powerful but diffuse light, such as supplied by the average examining light or pocket flashlight. It takes very little

practice for the examiner to become adept at holding the lens with the thumb and forefinger of the left hand, at the same time lightly elevating the upper lid with the fourth finger of the same hand. This leaves the right hand free for the removal of foreign bodies or for other manipulation.

A drop of 2 per cent aqueous solution of fluorescein instilled and then washed out of the conjunctival sac will aid the doctor in discovering many abrasions and ulcers of the cornea or conjunctiva.

The child with an eye injury presents a special problem when first examination by the family doctor reveals a perforation of the globe, or a suspicion of the same. Squeezing of the lids due to fright or pain or resistance to medication or attempt at lavage has on many occasions resulted in prolapse of intraocular tissues such as iris or vitreous, through corneal or scleral wounds. Once diagnosed, this type of injury, especially in very young or apprehensive or recalcitrant patients, should be handled as little as possible before being seen by the ophthalmologist. A sterile dry dressing should be applied and if possible the child should be hospitalized. At this point, avertin becomes the ophthalmologist's best friend. Prior to the advent of this drug I have seen, not infrequently, a simple corneal perforation converted into a gaping wound with prolapse of iris, vitreous or even lens as the result of a difficult induction during which the child struggled, squeezed the lids, or vomited.

The rectal instillation of avertin has the advantage of induction without any resistance on the child's part—even less than that encountered upon insertion of the needle for intravenous anesthesia. The child falls asleep in bed and the examination may be conducted without use of force or restraint. A few drops of cocaine 3 per cent, warmed to body temperature, may be instilled to further diminish sensitivity or reflex resistance. If it is found that surgery is necessary, intravenous or inhalation anesthesia may then be administered quietly while the patient is still under the influence of avertin, thus obviating the stormy induction which might have spelt disaster for the injured eye.

ADDITIONAL ARTICLE

ACUTE CORONARY ARTERY OCCLUSION AND DIABETIC ACIDOSIS WITH RECOVERY

LOUIS W GRANIRER, M D °

THE frequency of angina pectoris with glycosuria was reported as long ago as 1864, at which time Seegen,¹ a country doctor, suggested that all patients with this complaint have the urine examined for sugar. Coronary artery occlusion with diabetic acidosis, however, is a comparatively rare clinical entity. In a study of 890 attacks of coronary artery occlusion Master, Dack and Jaffe² noted that three had occurred with diabetic acidosis. Among 362 patients with diabetic acidosis treated at the Deaconess Hospital (Joslin³) there was only one case with a coronary artery occlusion.

The following case report is of interest because it shows the sudden onset of such a syndrome with several unusual features during the course of the illness.

A 53 year old white man was admitted to the Rockaway Beach Hospital on December 19, 1945, with a history of substernal pain of forty-eight hours' duration.

Past History—This was essentially unimportant with the exception of an attack of influenza in 1918. In 1942 the patient was told that he had a high blood pressure and in August of that year he experienced a slight "feeling" in the upper part of his chest while walking on the street, which lasted a few moments and disappeared after resting. A few months later he had two similar episodes, at which time he also developed a furuncle on the back of his left hand. He experienced no shortness of breath nor pain over the heart.

Family History—The patient's mother died at 92 from pneumonia and his father at 75 from cancer of the stomach. One brother died of carcinoma of the rectum at 46. Three brothers and one sister are living and well.

Present Illness—Six months before admission the patient was seized with a choking sensation in the right upper portion of the chest. He remained in bed for several weeks and then returned to work. Urine, blood count and electrocardiographic tracing were normal. He was well until two days before admission to the hospital when he experienced severe substernal pain radiating to his neck and down both arms. He complained of weakness and headache, had no desire for food, was very thirsty and nauseated, and he vomited. He had epigastric as well as chest pain.

Physical Examination—The patient was an alert, well developed and well nourished man, measuring 5 feet 5 inches in height and weighing 138 pounds. He

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had been in acidosis for thirty-six hours and was dyspneic. His cheeks were flushed and the lips were of good color, but his mouth was dry and parched, his tongue beefy and covered with a dry, encrusting debris. There was diminished intraocular pressure and an acetone odor to his breath.

The body temperature was 102°F , the pulse rate 125 per minute, and the respirations were 24 per minute. His muscles were flaccid and the tendon reflexes were diminished, the veins were poorly filled, and the blood pressure was 90 mm systolic and 60 mm diastolic. The rapid thready pulse, the low blood pressure and the scantily filled veins indicated vascular collapse.

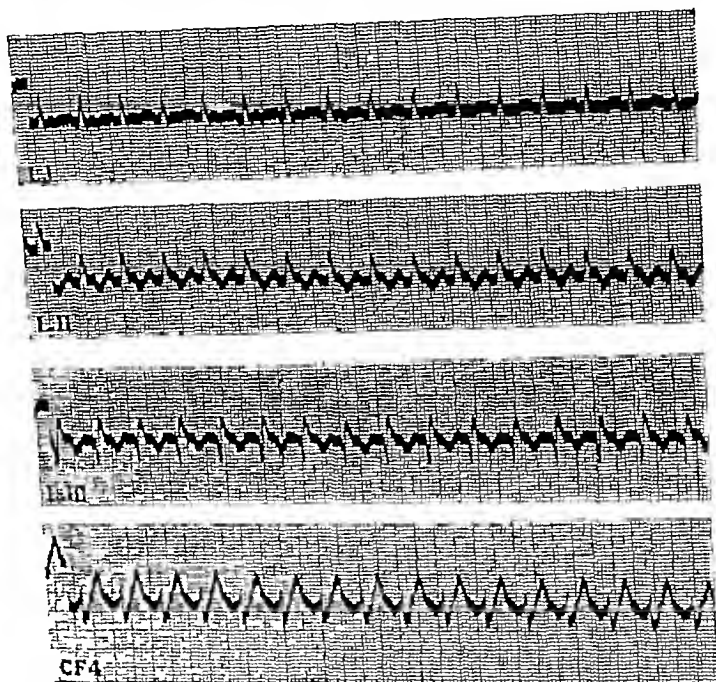


Fig 123 —This shows a high take-off and inversion of ST_2 and ST_3 typical of an acute posterior myocardial infarction

Chest The precordial dullness was increased to the left, no murmurs were heard. The heart sounds were rapid and distant and were obscured by loud rhonchi. There was diminished expansion over the left side of the chest.

Abdomen The liver was palpable three fingerbreadths below the right costal margin.

Neurological There was a blurring of both optic disks, all tendon reflexes were diminished.

Laboratory Study —The carbon dioxide combining power of the blood plasma was 20 volumes per cent. The blood sugar level was 528 mg per 100 cc, the non-protein nitrogen was 40.9 mg per 100 cc. There was a 4 plus glycosuria, and the urine contained large amounts of acetone and diacetic acid. There was a moderate albuminuria. Occasional hyaline and granular casts were found on microscopic examination of the urine. The blood count revealed hemoglobin 93 per cent, red

blood cells 5,800,000 and white blood cells 27,000 (polymorphonuclear leukocytes 87 per cent, lymphocytes 13 per cent)

The electrocardiogram showed a sinus tachycardia of 130, low QRS complexes and slurring in all leads, T_1 inversion, T_2 deep inversion, prominent Q_3 with an elevated ST_3 take-off and T_3 deeply inverted, absent R_4 with a low and abrupt take-off of ST_4 (Figs 123-125)

Diagnosis Coronary artery occlusion and diabetic acidosis

Treatment—Morphine sulfate was immediately administered subcutaneously in doses of 0.16 gm every four hours simultaneously with atropine sulfate 0.006. The patient was also given 0.1 gm papaverine hydrochloride intravenously. This was repeated every four hours as long as he was in shock or suffered pain (for

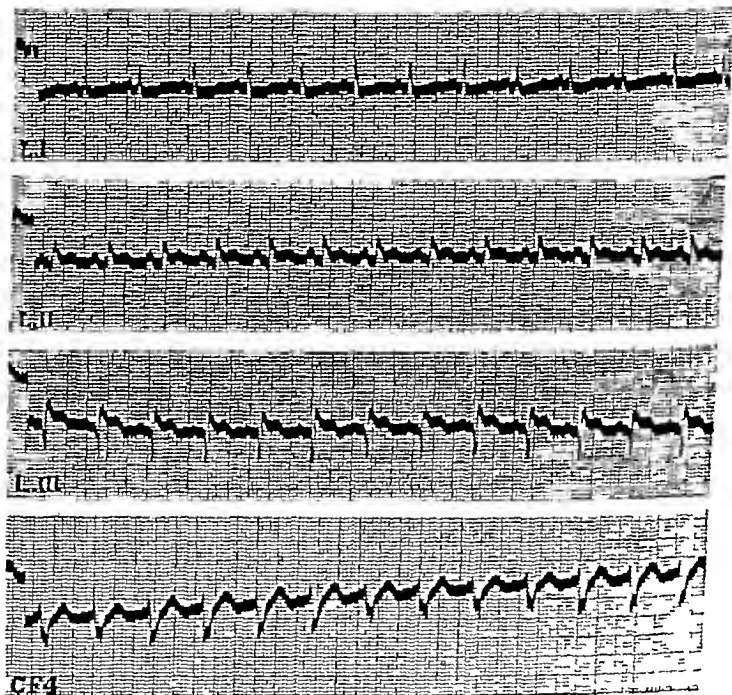


Fig 124—This shows T_2 and T_3 upright and still elevated, taken five days later

forty-eight hours) Oxygen was administered by means of a mask during this period. Subsequently he received aminophylline 0.2 gm with phenobarbital 0.016 gm three times a day.

For his diabetic condition he received 10 units of unmodified insulin subcutaneously at hourly intervals for the first four hours. Blood sugar levels, carbon dioxide combining power of the plasma, and urine for glucose and acetone were determined at frequent intervals until a satisfactory response was obtained. During the next eight hours it was necessary to give him 60 units followed by 100 units in the second twelve hours making a total of 320 units in twenty-four hours. One liter of normal saline solution was administered intravenously, at the rate of 300 cc per hour. Two liters of water and broth were administered by mouth. Thiamine hydrochloride 50 mg and vitamin C 200 mg were given every four

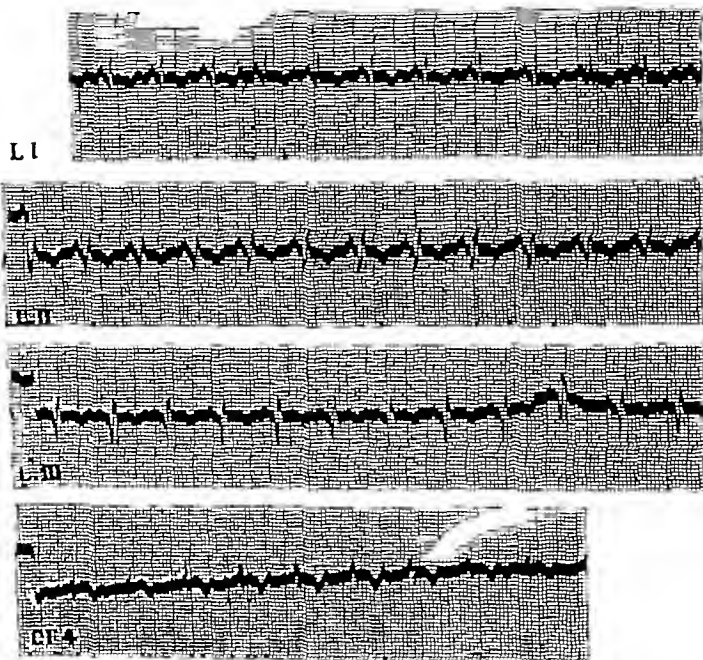


Fig 125—This was made one month later The T waves are inverted in all leads
Q₂ and Q₃ are prominent



Fig 126

hours As soon as he was able to take fluids by mouth, 200 cc of fruit juice or ginger ale were given every two hours The insulin was regulated by the urinary findings every three hours at first, then every four hours Solid foods were added gradually to the diet and after two days the usual three meal schedule was resumed, totaling for the day 250 gm carbohydrate, 75 gm protein, and 75 gm fat. One fifth of the carbohydrate diet was taken at breakfast, two fifths at lunch, two fifths at supper and a small midafternoon luncheon was given to avoid a hypoglycemic reaction

For three weeks the patient required 80 units of globin insulin daily which was administered one hour before breakfast. The urine was not allowed to become

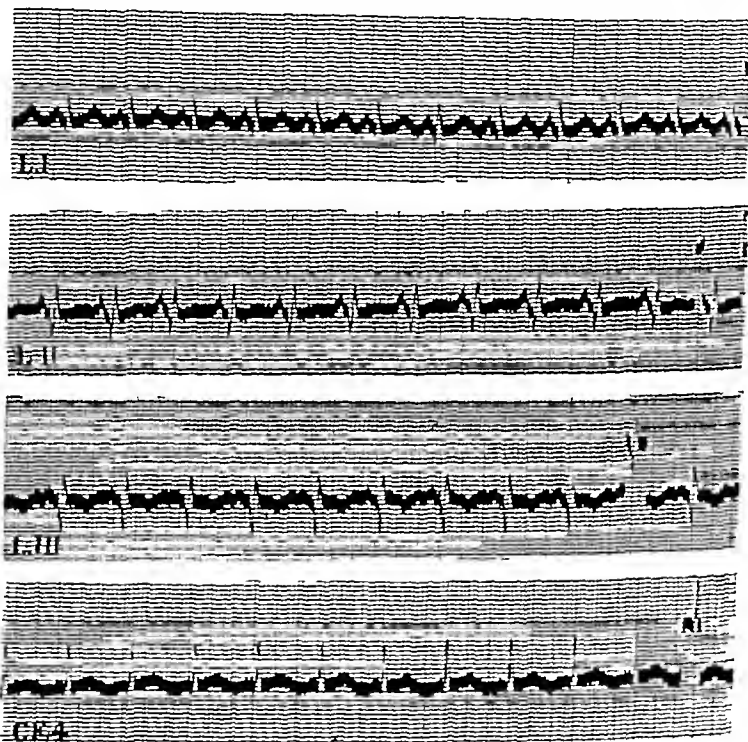


Fig 127—Graphic interpretation shows Q_2 and Q_3 are conspicuous, only T_3 is inverted

completely sugar-free There were no hypoglycemic reactions and there was apparently sufficient residual insulin action through the night to prevent excessive glycosuria and azoturia The insulin requirement became less and less The diet was supplemented with large doses of vitamin C and vitamin B complex When discharged on February 8, 1946, eight weeks after admission, the patient's urine was sugar-free without insulin Two hours after breakfast, the blood sugar was 210 mg per 100 cc of blood and his blood cholesterol was 300 mg per 100 cc of blood

On March 29, 1946, the blood sugar and blood cholesterol two hours after breakfast were 143 and 212 mg per 100 cc of blood respectively A 6 foot chest plate showed a heart within normal limits (Fig 126) The electrocardiogram at

that time showed a deep Q₂ and a low T₂, a deep Q₃ with T₃ inversion (Fig 127) The patient returned to work six months after the occlusion, but with restricted activities and under careful diabetic supervision He takes no insulin and is on a diet of 150 carbohydrate, 75 protein and 75 fat Six months after discharge from the hospital he developed a periarthritis of both shoulders which may have been caused by the prolonged bed rest This condition, however, may occur before as well as after a coronary thrombosis, and is probably due to an involvement of the cervical sympathetics

COMMENT

It has been shown that after a coronary artery occlusion a reflex occurs which tends further to decrease the blood supply to the infarcted region and to the remainder of the heart muscle This reflex vasoconstriction acts through the vagus nerve The use of atropine here is specific and with aminophyllin or papaverine the coronary circulation is improved⁴ The injured heart cannot long tolerate a low oxygen concentration and so oxygen must be supplied by mask or tent⁵ Cruickshank⁶ showed that the diabetic heart infused with diabetic blood does not utilize the blood sugar until insulin is added in physiological doses and that the diabetic heart does not react to insulin unless the blood sugar is kept well above normal In cardiac disease, also, the use of glucose and oxygen increases considerably the creatine phosphate of the myocardium⁷

During the acute phase of a coronary closure, there frequently occurs a disturbed carbohydrate tolerance The glycosuria may be only temporary and nondiabetic Raab and Rabinowitz⁸ studied a group of twenty-one patients with coronary occlusion and glycosuria Abnormal glucose tolerance curves observed during and immediately after the occlusion became normal later in 67 per cent of their group They believed that the transient glycosuria was caused by a disturbance of the vegetative nervous centers of the brain Hoff and Hausner⁹ were able to produce the same condition in dogs by tying off the coronary vessels In patients dying early of coronary closure, they found edema of the medulla and lower pons On the other hand, Cruickshank¹⁰ believed that the transitory glycosuria during coronary thrombosis was the result of reflex spasm of the already diseased vessels in the pancreas and the decreased insulin production accounted for the hyperglycemia and glycosuria He felt that these patients were potentially diabetic and that the glycosuria was temporary or permanent, depending upon how much injury was done to the pancreas In other words, the question of a true diabetes mellitus cannot be settled with certainty at the time of an attack of coronary thrombosis Davidson and his associates¹¹ found a correlation between peripheral vascular failure and abnormal carbohydrate metabolism, usually occurring in the older age groups There was no evidence of clinical diabetes in any patient after recovery High icteric indices and pro-

longed prothrombin times were present in most of their cases of medical shock and at autopsy an early central necrosis of the liver could be demonstrated

Coronary sclerosis and thrombosis are unusually frequent in diabetes, particularly in the mild and older diabetic. Atherosclerosis of the coronary vessels is the typical cardiac lesion in the diabetic. The diabetic with angina had a poor prognosis in 136 cases recorded by Root and Graybiel.^{12, 17} Half of the fatalities occurred during the first year after the onset of the angina, most of these patients, however, were poorly treated for their diabetes. Among 100 diabetic autopsies in the series of Nathanson¹³ there were forty-one subjects with extensive disease of the coronary arteries. Blotner¹⁴ found a similar proportion in his cases. Joslin¹⁵ noted that angina pectoris usually occurs on an average of nine years after the onset of diabetes and that the incidence trebles in the second ten years. Twice as many hypertensive diabetics are apt to have coronary disease as the diabetic with normal blood pressure. Moschcowitz¹⁶ is of the opinion that in arteriosclerosis there is an arteriocapillary fibrosis of the pancreas which is the cause of the diabetic state and hypertension.

Myocardial degeneration was found at autopsy in every case of diabetic coma reported by Foster.¹⁷ The short duration of life after the onset of angina pectoris in a diabetic is well explained by the severity of the coronary disease and myocardial changes found at autopsy.¹⁸ In a heart with gradually developing occlusions of the coronary vessel, however, the collateral circulation may compensate sufficiently to prevent appreciable myocardial damage.

In diabetic acidosis, the electrocardiogram shows definite changes. According to Stroud,¹⁹ the maximum abnormality develops twenty-four hours after the height of the acidosis and after the blood chemistry has returned to normal. There is lengthening of the QT interval, inversion of T_1 and T_2 with ST depressions. Usually the tracing becomes normal one week after the acidosis. Bellet and Dyer,²⁰ studying the electrocardiographic tracings of seventeen diabetic patients in coma, found T wave changes in every case, all the tracings became normal within a few days. In coronary occlusion with diabetic acidosis heart block may occur which may or may not be permanent. Blasdell²¹ reported in 1935 a very interesting case with transient heart block.

On the other hand, there is evidence that the diabetic heart suffers during hypoglycemia. Here there is a decrease in the amplitude of the T wave and displacement of the RT segment. Hypoglycemia may cause extrasystoles and even auricular fibrillation. Fishberg²² feels that ketosis is the only indication for insulin in diabetics with heart disease and advises hyperglycemia in the early phase of coronary

thrombosis The diabetic heart stores glycogen better with a blood sugar above normal whereas a rapid fall in blood sugar in such a heart may cause angina pectoris or even coronary occlusion

THERAPY

Several important points were brought out in the treatment of the case just reported

1 *A patient may be gravely ill with diabetic acidosis without actually going into coma* This fact has been emphasized by Albrecht²³ In 452 cases of diabetic coma summarized by Joslin (quoted by Albrecht²³) only 18 per cent were totally unconscious or in true coma In our case the prompt recognition of coronary occlusion in a patient with diabetic acidosis enabled us immediately to institute energetic treatment and a well ordered program of management of both conditions No detail was too small to be overlooked Occasionally the signs and symptoms of coronary thrombosis are masked by acidosis or coma Our patient was a mild or latent diabetic who was precipitated into diabetic acidosis by a myocardial infarction

2 *Too little insulin in the presence of diabetic acidosis can be a serious error* Death from diabetic coma is much more likely to occur from undertreatment than from overtreatment Hypoglycemia is usually unheard of in the first six hours of severe acidosis and intravenous glucose during this time is seldom indicated²⁴ In coronary thrombosis resistance to insulin may develop so that large doses are necessary There have been rare reports of cases where overdoses of insulin have precipitated angina pectoris in diabetics and occasionally a fatality has occurred The danger has been exaggerated and there should be no hesitancy in the use of insulin when heart disease is present A mild degree of hyperglycemia and glycosuria does no harm and increases the margin of safety Duncan²⁵ points out that urinary tract infections may lead to a disappearance or diminution of sugar in the urine even though there may be marked hyperglycemia

3 *Lost fluids and electrolytes must be adequately replaced in the tissues*

4 *Bed rest must be enforced for seven weeks* For the first ten days our patient was not permitted to move himself in bed and was given sedation to prevent restlessness He was kept on oxygen therapy for the first forty eight hours Dicumarol was not used It can be safely administered, however, to patients with coronary thrombosis Embolic phenomena may be reduced to one eighth and the mortality rate to one fifth as a result of the use of dicumarol as shown by a comparison of results in fifty patients who did and sixty who did not receive dicumarol Two hundred milligrams should be administered daily by mouth for a period of one month and the prothrombin time maintained

at between 30 and 35 seconds The dose of dicumarol may be reduced to 100 mg daily or every other day depending on the prothrombin time

5 *Complete healing of the myocardial infarction does not occur until at least three or four months have elapsed* Therefore, restricted activity for the first six months is necessary Careful control of the diabetes is very important, particularly when it accompanies a cardiovascular accident as in the case reported

SUMMARY AND CONCLUSIONS

A patient with coronary artery occlusion and diabetic acidosis presented a grave medical emergency requiring energetic treatment. Recovery followed the judicious use of insulin, diet and bed rest Our knowledge is still nebulous as to the frequent occurrence of cardiovascular disease in diabetes As Joslin has said, "It is not that the diabetes is bad, it's the company it keeps"

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SYMPOSIUM ON BLOOD TRANSFUSION AND RH FACTOR* OPERATION OF A BLOOD TRANSFUSION SERVICE

THOMAS H. SELDON

DURING the last ten years at the Mayo Clinic the number of blood transfusions per year has increased more than four times. In 1945, 5,187 transfusions were given by means of the indirect method of administering the citrated whole blood. The increase in number is indicative of the interest in, and the value placed on, blood transfusions. This condition is not a local one, but is general throughout the whole country. I believe the interest and value will be shown by greater numbers of transfusions as physicians and surgeons return from the military services.

Because of the importance placed on blood transfusion, it is felt that a symposium on the subject of blood transfusions is in order.

At the Clinic we have a blood transfusion service committee whose duty is to advise on all procedures and problems relating to the blood transfusion service. This includes problems of the actual operation of the blood bank, the arrangements necessary for procurement and care of blood donors and clinical pathologic laboratory work necessary for examination of blood. The clinical use and administration of blood transfusions and investigation of all transfusion reactions, particularly the more serious ones, also are part of the duty of this committee. The use of blood plasma and serum albumin follows the same routines as whole blood. Both of these products are valuable therapeutic agents when their use is indicated.

The blood bank is situated in the Medical Science Building which is convenient and practical for several reasons, namely, it is near to the Clinic for friends and relatives of patients, convenient for many of the Mayo Clinic by members of a blood transfusion committee.

professional donors, away from hospital atmosphere which sometimes frightens prospective donors and readily accessible for laboratory work. The bank is staffed by physicians, nurses, technicians and secretaries. It is open approximately twelve hours every day except Sunday. At the bank all records of donors' and recipients' blood groupings and Rh factors, as well as other pertinent facts about donors, are filed.

Cross matching of donors' and recipients' bloods, in most instances, is arranged through the blood bank.

All blood donors undergo phlebotomy at the blood bank. In most instances the blood of donors is taken at the bank for the necessary tests. All blood is drawn into vacuum bottles containing a special mixture of dextrose, sodium citrate and citric acid which permits storage of the blood for up to twenty-one days. However, blood is seldom kept that long before it is used. Regular deliveries of blood are made from the bank to the various hospitals at stated intervals during the day. Each hospital usually carries an adequate supply to meet its own emergency needs for transfusions but emergency deliveries are made from the bank if necessary.

At the blood bank ambulatory patients may be given blood transfusions and observed for several hours. This work is done in the afternoon when the bank is otherwise not particularly busy. In cases of polycythemia in which patients are ambulatory phlebotomy is carried out at the blood bank. If a hospitalized polycythemic patient needs to undergo phlebotomy it is performed in the hospital.

A physician from the clinical pathologic laboratory spends part of each morning in the blood bank supervising the interco-ordination of the two services.

Blood transfusions are actually administered under the direct supervision of the Section on Anesthesiology. Almost invariably all patients who have transfusion reactions are encountered first by physicians of the Section on Anesthesiology. They communicate with the physician whose patient has the reaction, and an arrangement is made for treatment of the patient's reaction. If it is desirable to obtain further consultation with the hematologist, clinical pathologist or both these are arranged by the physician or anesthetist. All transfusion reactions are recorded carefully in detail and discussed at the bimonthly meeting of the blood transfusion service committee. From these discussions certain information is obtained, treatment for future reactions is discussed and necessary changes in administration are proposed.

LABORATORY ASPECTS OF BLOOD GROUPING AND THE RH FACTOR

GEORGE G. STILWELL

THE laboratory aspects of the broad problem of the transfusion of blood involve many procedures and bear a close relationship to the clinical implications of the problem. Included among these laboratory procedures are the determination of the proper blood grouping of donor and recipient, cross-matching of the blood selected for transfusion, various tests to rule out diseases in the donor, determination of the Rh factor and Rh sensitization, tests to determine the bacterial sterility of blood and plasma, estimation of the longevity and efficacy of various components of stored blood and plasma, laboratory investigation of reactions to transfusion, and a host of others. This paper will be confined to a consideration of some of the basic laboratory principles which underlie blood grouping and the Rh factor, together with a consideration of cross-matching.

BLOOD GROUPING

The separation of human blood into four main groups depends on the presence or absence in the erythrocytes of two agglutinogens A and B, together with the presence or absence in the serum of corresponding agglutinins α and β . The agglutinogens are antigenic, whereas the agglutinins are antibodies. If an agglutnogen is brought into contact with an incompatible agglutinin, an antigen-antibody reaction occurs which results in clumping of the erythrocytes containing this agglutnogen. This antigen-antibody reaction is of the same general nature as that obtained from the various bacterial diagnostic agglutination tests.

Blood grouping in its simplest form is done by the bringing together of (1) erythrocytes of the person in question and (2) serum of known agglutinin content. The presence or absence of clumping of the erythrocytes will then determine the blood group. This mingling of serum and erythrocytes is most commonly done on flat glass microscope slides or on slides provided with shallow concave wells. Agglutination of the erythrocytes usually is visible to the unaided eye, but the appearance always should be checked microscopically. Another widely used method consists of the mixture of somewhat larger amounts of erythrocytes and serum in test tubes of small diameter. Agglutination is then observed macroscopically. The erythrocytes to be grouped are most conveniently handled in the form of a suspension made by the addition of two or three drops

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of whole blood to about 2 ml of saline-citrate solution. These suspensions of cells should be fresh and free from gross bacterial contamination. If contamination with bacteria occurs in the suspension of erythrocytes, panagglutination may be seen, with consequent faulty grouping. If blood cannot be examined for some time after collection, or when the specimen is to be mailed, it is best to place several milliliters of blood in a clean dry tube without anticoagulant. The blood is allowed to clot, the clot remaining in the tube in contact with the serum. Fresh suspensions of cells can then be made at any time up to two weeks by removal of a small amount of the clot and shaking it up with saline.

Two kinds of serum of known agglutinin content are necessary for the performance of blood grouping. One is group A serum, which contains the β or anti-B agglutinin. The other is group B serum, which contains the α or anti-A agglutinin. Grouping serum may be obtained from several sources. The serum of patients whose blood is being grouped may be saved and used for this purpose, if enough grouping is done each day to provide a fresh supply of potent serum. Professional donors whose serum contains agglutinins in high titer may contribute blood regularly to supply grouping serum. Soluble group-specific A or B substance may be injected into such persons to produce even higher agglutinin titers. Grouping serum of animal origin may be prepared by the injection of erythrocytes into laboratory animals, usually rabbits. This stimulates production of a specific agglutinin against the particular kind of erythrocytes used. This serum may be dried and sealed in ampules. It will maintain potency indefinitely in this state. When ready for use, the dried serum is dissolved in saline solution.

In many cases, blood grouping is carried out with the use of only the erythrocytes of the patient and known group A and group B serum. As a safeguard, it is advisable to determine also the agglutinin content of the patient's serum by testing it against suspensions of known A and B erythrocytes. This procedure acts as a check against the grouping determined by the use of erythrocytes alone, and is a safeguard against erroneous reports. More blood must be obtained from the person whose blood is being grouped, in order to provide the serum, but this disadvantage is more than outweighed by the benefit gained.

The routine blood grouping technique employed at the Clinic involves testing of both the serum and the erythrocytes of the patient against known A and B erythrocytes and serum, respectively. This is done on glass slides which contain three rows of shallow concave wells, with four wells in each row. A drop of group A serum is placed in the first well of a row and a drop of group B serum is placed in the second well. The grouping serum used in this method is obtained by saving

the serum derived during the process of grouping other patients A drop of the suspension of erythrocytes from the patient in question is added to each of these wells and is mixed with the serum A drop of group A erythrocyte suspension is placed in the third well, and a drop of group B erythrocyte suspension is placed in the fourth A drop of the patient's serum is added to each of these latter wells and mixed. The slide is examined microscopically for evidence of agglutination of the erythrocytes This agglutination begins to be evident almost at once, and usually is complete within two or three minutes. The blood group is determined by the presence or absence of agglutination of the erythrocytes, as shown in table 1

TABLE 1
DETERMINATION OF BLOOD GROUPS ON THE BASIS OF AGGLUTINATION
OR NONAGGLUTINATION OF ERYTHROCYTES

Group of Blood Tested	Serum		Erythrocytes	
	Group A	Group B	Group A	Group B
AB	+	+	-	-
A	-	+	-	+
B	+	-	+	-
O	-	-	+	+

+ = agglutination of erythrocytes
- = no agglutination

There must be complete and unequivocal agreement in the agglutination reactions seen in the four slide wells before a grouping is recorded. Each specimen of blood is grouped independently by two different persons, who use different sets of known serum and suspensions of erythrocytes. There must be complete agreement between these two independent determinations before a final report is made. Several factors may cause difficulty in blood grouping. Formation of rouleaux may sometimes be confused with true agglutination, whereas use of higher microscopic magnification generally will show the continuity of outlines of individual cells in rouleau formation, whereas in true agglutination the individual erythrocytes lose their cell outline and become tightly clumped in an amorphous mass. Dilution of the serum-erythrocyte mixture by three or four drops of saline usually will disperse the rouleaux, whereas agglutinated cells are unaffected by such an action. The use of suspensions of old erythrocytes or of

grouping serum which has decreased in potency may give rise to false negative reactions. It may be difficult or impossible to group the blood of newborn children because of the relatively low agglutinin content of erythrocytes in infants. In some instances, the agglutinin content increases so slowly that the grouping cannot be definitely established until the end of the first year of life.

Difficulties may arise because of the presence of subgroups of the A agglutinin. The A₂ agglutinin is much less agglutinable than is the A₁ type. Unless highly potent typing serum is used, agglutination of cells containing this A₂ agglutinin may easily be overlooked, and such specimens of blood may then be erroneously reported as belonging to group O. The same consideration applies to blood of group A₂B. If the weakly reacting A₂ component is not agglutinated by the grouping serum, such specimens of blood are erroneously reported as belonging to group B.

Most of the afore-mentioned difficulties can be obviated by grouping the patient's serum against suspensions of known group A and group B erythrocytes. As a rule, the use of this checking procedure is not helpful among infants, however, because the serum of infants may contain only agglutinins derived from the mother's circulation and may not contain any autogenous agglutinins.

THE RH FACTOR

The Rh factor was first described in 1940. It is an agglutinin which is present in the erythrocytes of approximately 85 per cent of Caucasian persons, regardless of their sex or primary blood group. The incidence of the Rh factor varies considerably in different races. It is important clinically, as emphasized elsewhere in this symposium, because certain persons who lack the Rh factor are capable of being sensitized to blood containing the Rh factor. The Rh-negative persons who are thus sensitized respond by producing antibodies against the Rh factor. Thus, the basic laboratory tests involved in the Rh factor include the determination of the presence or absence of this agglutinin and the detection of Rh antibodies in the serum of Rh-negative individuals suspected of being sensitized to the Rh factor.

Serum for use in determination of this factor may be of animal or human origin. The serum used in earlier phases of this work was derived from animals sensitized to the blood of Rhesus monkeys. All animal serums of this nature gave similar results when used in parallel tests. It was soon found, however, that serum of human origin was of three different varieties. One type of human serum corresponded to the original animal anti-Rhesus serum and gave reactions that were approximately 85 per cent positive. This was designated anti-Rh serum. Another type of human serum gave reactions that were 70 per cent positive, and this was designated anti-Rh'. The third type

TABLE 2
SUMMARY OF THE EIGHT RH BLOOD TYPES

Types Designation	Clinically Rh negative Persons (15 per cent)			Clinically Rh-positive Persons (85 per cent)		
	Reaction with Antiserum			Types, Designation	Reaction with Antiserum	
	Rh'	Rh''	Rh ₀		Rh'	Rh''
rh				rh ₀		
Rh'	-	-	-	Rh ₁ (Rh ₀)	-	-
Rh''	+	-	-	Rh ₂ (Rh ₀ '')	+	-
Rh Rh''	-	+	-	Rh ₁ Rh ₂ (Rh ₀ ' Rh ₀ '')	-	+
+	+	+	-		+	+
-						

+ = agglutination of erythrocytes
- = absence of agglutination

of human serum gave reactions that were 30 per cent positive, and was designated anti-Rh''

These three human anti-Rh serums containing specific agglutinins are used to detect the presence or absence of three corresponding antigens or Rh factors in human blood, designated Rh₀, Rh' and Rh'' By the use of all three of these serums, the blood of human beings can be classified into eight types or subgroups of the Rh factor as shown in table 2, by Wiener

There are four types of blood which, for clinical purposes, should be considered to be Rh-negative These are types rh, Rh', Rh'', and Rh'Rh'' Persons who have blood which is classed in any of these four divisions should be treated as Rh-negative persons when they are recipients of transfused blood or when they present obstetric problems concerned with the Rh factor This is not true, however, when these same people are considered as donors of blood Blood for transfusion as Rh-negative blood should be obtained only from persons whose blood is of type rh, because type Rh' or type Rh'' blood may cause reactions if it is transfused to persons who have become sensitized to these particular factors

TESTS FOR THE DETERMINATION OF THE RH FACTOR

For routine clinical purposes, it generally is necessary to make tests only with the standard anti-Rh₀ serum It is preferable to use serum of human origin This procedure will separate persons as having either Rh-positive or Rh-negative blood It has been suggested that this procedure be termed "Rh testing" It has been suggested, also, that the procedure of use of all three Rh antisera to classify human blood into the eight Rh types be termed "Rh typing"

The routine test employed at the Clinic for Rh testing is the rapid slide test of Diamond and Abelson, in which anti-Rh₀ serum of human origin is utilized Blood for this test may be collected as is blood to be used in the Westergren erythrocyte sedimentation rate test, by the addition of 2.7 ml of blood to 0.3 ml of a 3.8 per cent solution of sodium citrate The important element in this test is the use of a heavy suspension of erythrocytes, of approximately 50 per cent density.

Two large drops of the blood are mixed with one large drop of the testing serum on a glass slide This is conveniently done by thorough stirring of the serum and blood with the smooth round end of a small glass test tube, the mixture being spread on the slide over a circular area of about 1 cm in diameter The slide is gently tilted back and forth for two minutes and examined macroscopically for evidence of agglutination of the erythrocytes This test is best carried out by use of the tilting box recommended by Diamond and Abelson in their description of this rapid slide procedure This consists of a wooden

box mounted on an axis so that it can be tilted back and forth. A low-power electric bulb is enclosed, and the box is covered at the top by a piece of frosted glass. The bulb serves both to warm the slide containing the serum-blood mixture and to facilitate observation of the agglutination of the erythrocytes. The top of the box will accommodate a slide large enough for the simultaneous performance of six tests.

One great advantage of this rapid slide test is that it utilizes serum containing the blocking antibodies. This type of serum actually occurs more frequently than that containing regular anti-Rh agglutinins, but it formerly was considered to be worthless as an Rh testing agent. The other important advantage is that the procedure is simple and rapid; it allows examination of the blood of both patient and donor prior to transfusion.

If definite gross clumping of the erythrocytes is observed at the end of two minutes, the result of the test is considered positive, the blood of the patient is classified as Rh-positive, and no further tests are performed. If the test results in a negative or doubtful reaction, the blood is further examined by means of the standard test tube method, in which the three varieties of anti-Rh diagnostic serum (anti-Rh₀, anti-Rh' and anti-Rh'') are utilized. Small test tubes, with an inside diameter of 7 mm, are used. A drop of a fresh 2 per cent suspension of erythrocytes is placed in each of three tubes. One drop of anti-Rh₀ serum is added to the first tube, a drop of anti-Rh' serum is added to the second tube and a drop of anti-Rh'' serum is added to the third tube. The serum and erythrocytes are mixed and the tubes are placed in a water bath at 37° C for one hour. The tubes are then centrifuged for one minute at a speed of 1,000 revolutions per minute. The tubes are then carefully examined for evidences of agglutination of the erythrocytes, and the Rh classification is determined as shown in table 2.

TESTS FOR THE DETERMINATION OF RH SENSITIZATION

When Rh-negative persons are exposed to the Rh factor either by having Rh-positive blood transfused to them or by carrying an Rh-positive fetus, a certain number of them become iso-immunized. In response to the development of this sensitization, Rh antibodies appear in the serum of these persons. Several tests have been developed to demonstrate the presence of these antibodies.

Agglutination Test—This was the first test used to detect the presence of Rh antibodies. It was somewhat disappointing in the fact that it gave a positive result in a relatively low number of patients who had clinical evidence strongly suggestive of Rh sensitization. Moreover, there was no apparent correlation between the titer of antibodies found in this test and the clinical severity of the sensitization.

Erythrocytes of known Rh type are essential to performance of this test. Under ideal conditions, it is necessary to have available group O blood of types Rh₁, Rh₂, and rh. Fresh suspensions of erythrocytes are made by washing of the cells once and the addition of enough saline to make approximately a 2 per cent suspension. Serial saline dilutions of serum suspected of containing anti-Rh agglutinins are made so that they range from pure serum to a dilution of 1/64. Place three rows of small tubes with an inside diameter of 7 mm. in a rack. Place a drop of the undiluted serum into the first tube in each row. Place a drop of the 1/2 saline dilution of serum into the second tube in each row, into the third tube of each row place a drop of the 1/4 saline dilution of the serum. Continue until the 1/64 dilution of serum is reached.

Add a drop of the suspension of Rh₁ erythrocytes to each of the tubes in the first row, to each tube in the next row add a drop of the suspension of Rh₂ erythrocytes, and to each tube in the last row add a drop of the suspension of rh erythrocytes. Shake the tubes to insure adequate mixing, and incubate in the water bath for one hour at 37° C. Centrifuge the tubes for one minute at 1,000 revolutions per minute, and examine the sediment for evidence of clumping. The tubes are shaken or tapped very gently so as to dislodge the erythrocytes in the bottom. If strong agglutination occurs, the erythrocytes will be dislodged at the first tap in a large clump. Weaker agglutination will cause smaller aggregates of erythrocytes to appear. If no agglutination is present, it is difficult to dislodge the erythrocytes, and additional gentle tapping will cause them to swirl in an even suspension with no appearance of clumping.

When no agglutination occurs in any of the tubes, it is concluded that there are no anti-Rh agglutinins in the serum being tested. If agglutination occurs only in tubes containing type Rh₁ erythrocytes, then the serum contains agglutinin anti-Rh'. Agglutination occurring only with type Rh₂ erythrocytes indicates the presence of anti-Rh" agglutinin. If agglutination occurs with both type Rh₁ and Rh₂ erythrocytes, but not with type rh erythrocytes, then the agglutinins may be anti-Rh₀, anti-Rh₀', or anti-Rh₀". To classify further the agglutinins in this case, it is necessary to utilize a serum containing known potent anti-Rh₀ blocking antibodies. Mix one part of this blocking serum with five parts of the patient's serum, and repeat the entire test. If now there is no agglutination in any of the tubes, the serum contains agglutinin anti-Rh₀. If only type Rh₁ erythrocytes are clumped, the serum contains agglutinin anti-Rh₀'. If only type Rh₂ erythrocytes are agglutinated, the serum contains agglutinin anti-Rh₀".

For routine clinical purposes in determination of the presence or absence of Rh sensitization, it probably is not essential always to use known Rh₁ and Rh₂ erythrocytes. The routine procedure at the Clinic is to select at random three Rh-positive specimens of blood and one sample of type rh blood from the daily flow of samples of blood on which Rh determinations have been carried out. This selection ordinarily will include all the Rh antigens which are likely to be involved in the production of anti-Rh agglutinins. The tubes are set up and read in the same manner. When no agglutination occurs, the result of the test for Rh sensitization is concluded to be negative. If agglutination is seen, the result of the test is reported as positive, and the titer of antibody is determined by the highest dilution of serum which produces definite clumping of the erythrocytes. If agglutination still is present in the 1/64 dilution of serum, additional dilutions are used until an end point is reached.

Conglutination Test.—Because of the relatively unsatisfactory results obtained by testing for the presence of anti-Rh agglutinins in persons suspected of being sensitized to the Rh factor, a different test was devised and was designated by Wiener as the “conglutination test.”

This test is based on the presumption that there are two different kinds of Rh antibodies. One is the ordinary anti-Rh agglutinin detected by the use of the afore-mentioned saline suspensions of Rh positive erythrocytes. The other type of Rh antibody is the blocking antibody or glutinin, and its presence can be detected only in plasma or serum media. According to Wiener, when serum containing this type of Rh antibody is mixed with saline suspensions of Rh positive erythrocytes, the antibodies “coat” the erythrocytes but no agglutination occurs. A third component, present in plasma or serum, is necessary for agglutination. This component is called “conglutinin,” and probably is a colloidal aggregate of plasma proteins. The conglutinin is absorbed by the specifically sensitized erythrocytes, and it then causes agglutination. Because the conglutinin essential for this reaction is very easily dissociated into its component protein molecules by even slight dilution of the plasma with any crystalline solution, it is necessary assiduously to avoid the use of saline in the preparation of the suspensions of erythrocytes and the serum dilutions used in the performance of the test.

The conglutination test as done at the Clinic is performed in exactly the same manner as is the test for Rh agglutinins, with the exception that the suspensions of known Rh erythrocytes and the dilutions of the serum being tested are made up in AB plasma. The mixtures of serum and erythrocytes are placed in tubes, shaken vigorously and incubated in the water bath at 37° C for one hour. The tubes are centrifuged for one minute at 1,000 revolutions per minute, and are then examined for evidences of agglutination. The conglutination reaction usually is somewhat more difficult to detect than is the agglutination reaction. The tubes are agitated more during the reading of the conglutination test and the macroscopic appearance of the erythrocyte sediment pattern is not so reliable in this test as it is in the agglutination test.

The routine procedure in use at the Clinic is to perform the conglutination test first, with use of AB plasma obtained from the blood bank. If the result of this test is negative, it is concluded that there is no demonstrable evidence of Rh antibodies, and no further testing is done. If anti-Rh conglutinins are found, then a test for ordinary anti-Rh agglutinins is done.

CROSS-MATCHING

It is advisable and strongly recommended that cross-matching of the blood of the recipient and the blood of the prospective donor be done before blood is transfused. This will guard against the administration of incompatible blood, whether incompatibility is due to tech-

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nical errors in blood grouping, clerical errors in recording the grouping, accidental interchange of serums and blood samples, or the development in the patient's serum of unusual and irregular agglutinins

Cross-matching tests involving the mixture of the patient's serum and the donor's erythrocytes on a slide at room temperature ordinarily will reveal only gross incompatibility of blood and are not likely to disclose the presence of some of the more delicate irregular agglutinins. A more complete and satisfactory method of cross-matching includes the use of mixtures of serum and erythrocytes in test tubes at various temperatures

The routine cross-matching test at the Clinic involves the use of nine small test tubes which have an inside diameter of 7 mm. These tubes are set up in a rack in three rows, each row containing three tubes. Serum from the prospective donor is obtained from the pilot tube furnished by the blood bank. A suspension of the donor's erythrocytes is made by the plunging of a capillary pipet into the clot in the pilot tube, aspiration of a small amount of material, and shaking in 2 or 3 ml. of saline in a small tube. The tube is then centrifuged for several minutes, the supernatant saline is removed by aspiration and the erythrocyte sediment is resuspended in enough saline to make approximately a 2 per cent suspension. Fresh blood is obtained by venipuncture from the recipient. A few drops are used to make a 2 per cent suspension of erythrocytes in the same manner as detailed previously herein, and the remainder of the blood is allowed to clot so that serum may be obtained

Two drops of the patient's serum are placed in all three tubes, in both the left and right-hand rows. Two drops of donor's serum are placed in each of the three tubes in the center row. One drop of the saline suspension of donor's erythrocytes is added to each of the first two tubes in the left-hand row. One drop of the saline suspension of the patient's erythrocytes is added to each of the first two tubes in the center and right-hand rows. To the third tube in the left-hand row is added a drop of donor's erythrocytes suspended in donor's serum. This is made by the mixing of a small amount of material, obtained by plunging a capillary pipet into the clot in the donor's pilot tube, with a small amount of the donor's serum. To the third tubes in the center and right-hand rows is added a drop of the patient's erythrocytes suspended in the patient's serum. This suspension is made in the same manner as the suspension just described. The avoidance of saline in each of the tubes in the last row duplicates the conditions of the conglutination test, and allows the demonstration of conglutinating antibodies, if such should be present.

The front row of tubes is placed in a refrigerator, the second row of tubes is kept at room temperature, and the third row of tubes is placed in a water bath at 37° C. At the end of an hour all tubes are examined for agglutination of the erythrocytes

The left-hand row of tubes containing the mixture of patient's serum and donor's erythrocytes constitutes the major cross-match. This is the most important part of the procedure, because agglutinins in the patient's serum causing clumping of the donor's erythrocytes are by far the most important factor in hemolytic reactions to transfusion. If there is either gross or microscopic evidence of agglutination in these tubes, especially in those kept at room temperature and at 37° C, while no agglutination occurs in the tubes containing a

mixture of the patient's serum and erythrocytes, the cross-matching is termed unsatisfactory and the donor is rejected

The center row of tubes containing the mixture of donor's serum and patient's erythrocytes makes up the minor cross-match. Clumping of the patient's erythrocytes due to agglutinins present in the donor's serum will be detected here. These agglutinins usually are of no great importance as a cause of hemolytic reactions because of the dilution of the donor's serum during the course of the transfusion. They may give rise to trouble if they are of unusually high titer, or if the blood is administered too rapidly.

The right-hand row of tubes containing the mixture of patient's serum and erythrocytes is used for the detection of auto-agglutinins. These tubes serve as a control in the interpretation of agglutination occurring in the major cross-match. In some instances, information obtained in this control series of tubes has allowed the use of blood which otherwise would have been deemed unsatisfactory.

The tubes are placed at three different temperatures to bring out the presence of all possible agglutinins, some of which are much more active at certain thermal levels than at others. The first row of tubes is placed in the refrigerator to increase the chances of detection of autohemagglutinins. These agglutinins cause the patient's serum to agglutinate his own erythrocytes as well as many other erythrocytes of the same group or different groups. Auto-agglutinins are most active at low temperatures, and their significance is largely unknown. They are especially prominent in atypical pneumonia caused by viruses, but they may occur in a variety of other conditions.

The second row of tubes, which is kept at room temperature, will indicate primarily agglutination due to the presence of the natural isohemagglutinins for A and B agglutinogens. Thus, agglutination caused by major group incompatibility will be evidenced at this temperature. These tubes will also display agglutination of the erythrocytes caused by autohemagglutinins of broad thermal amplitude or of high titer.

The third row of tubes is incubated at body temperature. In these tubes will be detected primarily the immune isohemagglutinins resulting from various types of iso-immunization of the patient. These are the irregular agglutinins which are not normally present in serum. They are warm agglutinins, and are much more readily demonstrated at body temperature. Included among them are the anti-Rh agglutinins and congenitins. Saline is not used in the mixtures of serum and erythrocytes in this row of tubes. Thus, blood incompatibilities due to Rh antibodies of the congenitinating type are readily demonstrable in this cross-matching technic. Other agglutinins which may cause clumping of erythrocytes at this temperature are auto agglutinins of extremely high titer or wide thermal ampli-

tude, sub-group hemagglutinins anti-A₁, and anti-A₂, and anti-O agglutinins

This cross-matching procedure probably is complete enough to detect practically all the hemagglutinins which are important enough to cause hemolytic reactions to transfusion. The information obtained from performance of this procedure is well worth the slight delay it may cause in administration of the blood. There are occasional conditions of dire emergency in which immediate transfusion of blood without preliminary cross-matching is necessary, but in the great majority of cases cross-matching should be considered as a routine preliminary to the administration of blood.

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THE RH FACTOR IN RELATION TO TRANSFUSION OF BLOOD: ITS IMPORTANCE IN OBSTETRICS

ARTHUR B. HUNT

APPROXIMATELY 15 per cent of Caucasians are Rh-negative. That is, their blood congenitally lacks the Rh factor, which is an antigen. This antigen is an agglutininogen. Rh-negative individuals, and hence Rh-negative pregnant women, run the risk of being sensitized, or iso-immunized, to the Rh factor when they receive a transfusion of Rh-positive blood. This sensitization consists of the tendency of anti-Rh agglutinins to develop in the recipient's blood and if, later, more Rh-positive blood is administered, anti-Rh agglutinins will cause agglutination of the Rh-positive erythrocytes so administered. This causes a serious transfusion reaction similar to, although less often fatal than, reactions caused by incompatibility based on the four blood groups.

There is a second way in which Rh-negative pregnant women may become sensitized, or iso-immunized, to the Rh factor. It is this: The Rh factor, or antigen, in the blood of a mother's own Rh-positive fetus somehow gains access to the maternal circulation. This type of Rh sensitization seldom has a deleterious effect on the mother unless she is subsequently given a transfusion of Rh-positive blood. However, irrespective of transfusion, pregnancy may sensitize her to the Rh factor, so that infants born in subsequent pregnancies may be seriously affected by a disease variously known as "hemolytic icterus and anemia of the newborn," "erythroblastosis foetalis" or "congenital hemolytic disease." Cause of this disease is that, during the latter part of pregnancy, anti-Rh agglutinins have passed readily from the maternal circulation to the fetal circulation and have attained therein a high concentration (or titer). These anti-Rh agglutinins cause the erythrocytes of the baby to undergo agglutination and, apparently, hemolysis which, in turn, bring about more or less profound anemia and jaundice. The infant, because of its anemia, apparently receives a tremendous stimulus to produce new, immature erythrocytes, among which erythroblasts commonly are seen. The clinical syndrome may vary all the way from mild jaundice and anemia to generalized edema of the newly born infant. The latter condition is known as "fetal hydrops" and infants to whom the term can be applied usually either are stillborn or die a short time after birth.

Unfortunately, there is no known specific cure or arresting treatment that can be applied during pregnancy to prevent congenital

hemolytic disease. Also, unfortunately, the condition usually, although not invariably, becomes more severe with each successive pregnancy until the affected infants are stillborn or die soon after birth. Death of seriously affected infants occurs in spite of treatment, which consists of transfusion of blood.

Women whose children may escape the unfortunate train of events described in the preceding paragraph fall into two small groups. The first is composed of those who may continue to give birth to affected infants but among whom the disease does not increase in severity with successive births. In such cases, when proper treatment is given to the infant in the neonatal period, the chances for its survival are good. An extraordinary case in point will be reported briefly.

CASE 1—A woman was delivered of her second infant in a place where facilities were not fully developed and it died about two weeks post partum. This occurred in the early days of availability of information concerning the Rh factor but the local physician was alert to the situation and identified the cause of the infant's death. Subsequently, still in her home community, this mother bore two infants, in examination of whom frank signs of congenital hemolytic disease were found soon after their birth. They were referred to the Clinic and survived after appropriate treatment administered in the Section on Pediatrics. The woman was delivered of a fourth erythroblastotic infant, this time on the obstetric service of the Clinic, this child likewise survived on treatment administered by the pediatricians.

The second of the two fortunate groups here under consideration is exemplified by the woman who, in a series of pregnancies, is delivered of an Rh-negative infant. The husband of such a woman must of necessity be heterozygous as to the Rh factor. A heterozygous individual is one whose body cells contain both the dominant Rh-positive and the recessive Rh-negative genes but whose germ cells after maturation contain only one or the other. If the ovum is fertilized by a sperm containing the Rh-negative gene the infant will be Rh-negative.

There is a third effect of sensitization of childbearing women, or potentially childbearing women, on which I should especially like to dwell in this communication. Any Rh-negative female infant, girl or woman who because of her age has present or future possibilities of childbearing, runs the risk of being sensitized to the Rh factor if she receives Rh-positive blood, just as is true of any other Rh-negative individual. This cannot be emphasized too strongly. The first fetus born to a woman who thus has been artificially sensitized to the Rh factor often has severe erythroblastosis. Frequently such babies are either stillborn or are so severely affected that their lives cannot be saved by correct treatment. It becomes readily apparent, then, that the entire obstetric futures of a number of young Rh-negative women throughout the country may have been placed in jeopardy or actually

ruined by their unintentionally having been given Rh-positive blood by transfusion. The percentage of Rh-negative women who become sensitized to the Rh factor by pregnancy is low—from 2 to 5 per cent of those who become pregnant, or slightly more, depending on the number of pregnancies they undergo. Of those who receive blood by transfusion the percentage sensitized to the Rh factor however, may prove to be much higher.

Accordingly, in the Section on Obstetrics and Gynecology we have become concerned about Rh-negative patients who have been inadvertently sensitized to the Rh factor by receiving Rh-positive blood in transfusion. Some of these women already have been delivered and their infants have died in spite of correct treatment. Others are still pregnant and we fear concerning the welfare of their babies because the blood of the women has been found to contain anti-Rh agglutinins. Some of these women, from their reading of articles written for laymen, are aware of their predicament and of its cause.

Two additional brief reports of cases will illustrate the general situation.

CASE 2—In 1936, because of severe anemia, a young woman who was in her first pregnancy received a transfusion here at the Clinic without untoward event. The pregnancy terminated normally and the child, who now is ten years of age, was and is normal. Three years later another normal delivery occurred. The infant, however, soon became jaundiced and anemic. The baby failed rapidly and, in spite of splenectomy, died in a few days. Shortly after this delivery, knowledge concerning the Rh factor and its role in the production of erythroblastosis became available. The patient was called in and her blood was found to be Rh-negative. It was suggested to her that future pregnancies probably would end disappointingly but the patient elected to undergo another pregnancy in two years. By breech extraction she was delivered (with some difficulty due to fetal hydrops) of a child which died in a few minutes. The placenta shared in the generalized edema, it was nearly 3 inches (7.6 cm) thick and filled a wash basin of standard size. In the decade since this patient's probable sensitization to the Rh factor, one of her sisters has been delivered of seven babies on our service and another of her sisters, who has been married for about four years, is approaching term in her second pregnancy.

CASE 3—A woman, thirty-two years of age, was admitted to the hospital in February, 1946, three days post partum, because her child was being admitted with congenital hemolytic disease. The woman had been pregnant two years before and had been delivered, elsewhere, of a normal infant. She had required transfusion, however, because of severe postpartum hemorrhage. The blood of this patient proved to be Rh-negative and her blood titrated for anti-Rh agglutinins sufficiently strong to make her suitable as a donor for testing serum. The infant died of congenital hemolytic disease in spite of correct treatment.

Two or three other facts should be emphasized about this matter of danger to the success of pregnancies for young Rh-negative women who have received Rh positive blood. It is true that an individual may resist sensitization with Rh-positive blood and cannot be sensitized

even by many transfusions of such blood *but there is no way of knowing in advance which patient will and which will not be affected* Therefore, first, the only safe policy is, in so far as possible, to use only Rh-negative blood for transfusion of all Rh-negative patients Second, once sensitization has been effected, the physician is powerless, at this time, to undo the harm caused by any treatment administered to the recipient Third, provided that enough dependable serum for testing for the Rh factor is available, that adequate laboratory service is at hand, and that enough Rh-negative blood can be supplied, the occurrence of obstetric difficulties arising from administration of Rh-positive blood to Rh-negative women is unnecessary It is recognized that the important facilities noted are difficult to maintain and that to maintain them throws heavy responsibility on physicians who are responsible for clinical laboratories and on those whose duty it is to supply blood for transfusion

Members of the transfusion service are constantly mindful of the danger of sensitizing Rh-negative individuals, especially women of childbearing age or less We of the Section on Obstetrics and Gynecology are grateful to them for their co-operation in this phase of our work as well as in treatment of the massive hemorrhages that occur at times in obstetrics We know, too, that the pediatricians are alert to the possible risks of giving Rh-positive blood to Rh-negative female children However, because future risks are likely to be forgotten by the best of men in the presence of imminent emergency, my colleagues and I believe that it is timely to remind internists, surgeons and all physicians who may be a party to transfusion of Rh-negative patients, especially of females from birth to the early forties of life, that untoward obstetric effects can result therefrom

TRANSFUSION REACTIONS AND THEIR TREATMENT

MALCOLM M HARGRAVES

Four types of transfusion reactions may occur, alone or in combination, these are pyrogenic, allergic, hemolytic and "overloading" reactions. Each type of reaction has its cause and treatment so that each can be considered in its turn.

PYROGENIC REACTIONS

The pyrogenic reaction is usually due to introduction of extrinsic pyrogens into the patient's blood stream by means of improperly cleansed equipment or contaminated water. While the causative agent is not definitely known it would seem to be a waterborne bacterial product which is not inactivated by heat during sterilization. These pyrogens may be sterile contaminants in the anticoagulant solutions used in the transfusion or they may have been left in the bottle, tubing or needle after they were washed or rinsed with water containing the pyrogens.

The pyrogenic reaction may be very mild and cause no complaint or it may be very severe and cause a shaking chill followed by high fever. Occasionally a heat stroke syndrome may develop, the temperature control mechanism failing to function. As a result fever of alarming proportions may occur and the patient may go into a semicomatose or comatose state.

Occasionally in a case of extensive infection, malignancy or thrombi, intrinsic pyrogens may be released when the blood volume is increased as the result of transfusion.

Obviously, prevention is the best form of treatment and it may be best accomplished by using pyrogen-free solutions and equipment. These solutions are best purchased from a manufacturer specializing in pyrogen-free materials. At the Clinic we have reduced such reactions by using pyrogen-free, disposable equipment, including bottle, tubing and needle. They are discarded after initial use. If equipment is to be reused it must be cleaned immaculately and then rinsed thoroughly with pyrogen-free water.

The possibility of releasing intrinsic pyrogens may be reduced by slow transfusion of the blood so that change in blood volume will be minimal.

In case of a mild pyrogenic reaction little more than symptomatic treatment is indicated with the judicious use of acetylsalicylic acid (aspirin), application of external heat during the chill and tepid sponging after the chill. In case of severe hyperpyrexia, heroic meas-

ures may be necessary to reduce the fever and save the patient from serious damage. Under such circumstances the patient does not sweat, hence, heat is not dissipated from the surface of the body by evaporation. This natural physical means of heat reduction may be employed artificially by directing the draft from an electric fan over the patient's body after he has been covered with a wet sheet to provide an evaporation surface. Ice packs can be used in addition to this if necessary. It must be understood that uncontrolled hyperpyrexia may be fatal.

ALLERGIC REACTIONS

Allergic reactions may be manifested by urticarial, edematous, asthmatic or anaphylactic phenomena. Urticaria may be troublesome but is not serious, whereas localized edema about the larynx could present an emergency that might require tracheotomy. Anaphylactic shock, of course, could be fatal.

Prevention of allergic reactions is not always possible, but some precautions can be taken. When the patient gives a past history of allergy the physician should be on guard when contemplating a transfusion. If time permits, the patient may be prepared by giving him 50 mg. of benadryl (beta-dimethylaminoethyl benzhydryl ether hydrochloride) or pyribenzamine hydrochloride (N'-pyridyl-N'-benzyl-N-dimethyl-ethylene diamine hydrochloride) four times a day for one or two days preceding administration of blood. Since the reaction of the patient is due to sensitivity to some allergen in the donor's blood, many potential allergens undoubtedly can be eliminated by using blood only from a fasting donor. Also it is wise not to use blood from a donor more than once since sensitivity to some specific protein in the donor's blood may have developed.

The injection of a 1:1,000 solution of epinephrine is usually helpful in combating an allergic reaction of minor or moderate degree.

In case of anaphylaxis, profound shock and collapse or death of the patient may occur. Again, epinephrine should be used, together with other stimulants and measures to combat shock—that is, application of external heat and administration of plasma or more blood to maintain blood volume and blood pressure.

HEMOLYTIC REACTION

The hemolytic reaction carries a mortality rate of 50 per cent. It is the most important reaction to be considered since so many possible factors enter into its production and prevention. This reaction may be due to the introduction of (1) incompatible blood cells into the recipient's circulation and their consequent hemolysis, (2) high titer, heterologous serum from a group O donor and consequent hemolysis of the recipient's own cells or (3) free hemoglobin from old hemolyzed blood.

Prevention of a hemolytic reaction always must be uppermost in the minds of any transfusion team. Checks and double checks should be made to eliminate all technical and human errors which might permit a patient to receive the wrong blood.

The symptoms of a hemolytic reaction should be recognized promptly so that the transfusion can be stopped as soon as they begin. Most commonly the patient will complain of progressively severe back pain in the lumbar region—usually this will begin after from 50 to 75 c c of blood has been introduced. The next most common complaint is of substernal pain or oppression, perhaps with dyspnea and anxiety. A shaking chill may be the first sign of hemolysis, although it occurs most commonly in the course of a pyrogenic reaction, and for that reason it is best to halt transfusion if a shaking chill develops.

If hemolysis has occurred and the immediate result has not been shock and death, delayed reactions may be expected. Jaundice usually follows hemolysis because the liver is unable to remove all of the released blood pigments. Oliguria usually ensues and this may be followed by anuria, azotemia and finally death. While it has been thought that renal damage results from the precipitation of acid hematin in the kidney tubules it is very likely that acute nephritis is produced by the free hemoglobin or its products.

Little, if any, treatment is of benefit. Alkalinization of the urine by bicarbonate solutions given intravenously and orally has long been used to prevent precipitation of acid hematin in the kidney tubules and it is probably worthy of continued use.

CARDIOVASCULAR FAILURE

Cardiovascular failure is due to failure of the right side of the heart and usually occurs in the case of the aged patient as the result of too rapid administration of the blood and fluids (overloading). Since pulmonary edema results, the symptoms are dyspnea, cyanosis and moist râles in the lungs. While the prompt withdrawal of blood by phlebotomy may be resorted to, tourniquets on all four extremities should be used to reduce the volume of circulating blood. These tourniquets should be applied for a few minutes, then released successively to permit some circulation in the extremity before again tightening them. This procedure can be carried out until the circulatory embarrassment has passed.

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THE TRANSFUSION OF BLOOD: INDICATIONS AND CONTRAINDICATIONS

J M STICKNEY

WHOLE blood is made up of many fractions, each of which has an important function. The preservation and storage of blood affect some of the component parts adversely. Any decision to introduce all or part of human blood into the vascular system of a patient requires some knowledge of what the patient needs and the suitability of the transfused elements. The procedure of transfusion involves a definite risk, even under the best of circumstances.

The principal components of blood are seven. First are erythrocytes, which contain an agglutininogen specific for their type which must always be compatible with the agglutinins in the plasma of the recipient. Erythrocytes are the only source of hemoglobin, which is the oxygen-carrying element in blood. Next are leukocytes, which disintegrate rapidly in stored blood. They play no recognized part in the transfusion of blood. Third are platelets, which disappear within a very few days when blood is stored. Except when there is a deficiency of platelets, they may be disregarded. Fourth are proteins, which are essential nutritional elements and are preserved in plasma and serum, no matter how blood is stored. Recently, much progress has been made in the separation of many of the proteins of the blood, but at present, except for gamma globulin, the protein fractions are not readily available. Fifth is prothrombin, which disappears quantitatively from stored blood or liquid plasma. Fresh plasma or frozen and desiccated plasma made from fresh plasma probably contains 50 to 75 per cent of its original content of prothrombin. Sixth are other coagulation factors. From a practical standpoint, the storage of blood or plasma makes little difference in these factors. The antihemophilic globulin is present in whole blood and fresh or desiccated plasma. Finally, there are immune bodies. Storage of blood or plasma causes little change in the recognized values of these components. Pooled plasma may offer some therapeutic advantage in that more antibodies may be included in it.

At the Clinic there is available routinely whole blood, fresh and desiccated plasma, and salt-poor serum albumin. The plasma from 500 c.c. of whole blood is considered one unit, and when it is desiccated, it may be dissolved in 50 to 250 c.c. of distilled water. The serum albumin is available in 5 gram units in 20 c.c. of solution. Erythrocytes suspended in isotonic solution of sodium chloride may be prepared when necessary. Two blood substitutes, 8 per cent solu-

tion of gelatin and 6 per cent solution of acacia in isotonic solution of sodium chloride, are also available

Thus far I have spoken of materials. In the material which follows I shall summarize the principles which usually are followed in a consideration of the value of the transfusion of blood. Chronic anemias which will respond to iron or to specific treatment seldom require transfused blood unless surgery is demanded before treatment can be effective. In hypochromic anemia and iron-deficiency anemia with good regeneration the administration of 15 to 20 grains (1 to 1.3 gm.) of ferrous sulfate daily generally will cause a prompt and continuous increase in values for hemoglobin. Since this type of anemia develops slowly, a value for hemoglobin as low as 4 to 5 gm. per 100 c.c. may be tolerated by the patient without unusual distress. At these levels, however, the transfusion of whole blood may be of aid in the more rapid restoration of a patient's condition to normal. When chronic loss of blood is a factor, the bleeding should be stopped as soon as possible. If no further loss or destruction of blood occurs, and the blood volume is unchanged except by the added blood, the transfusion of 500 c.c. of whole normal blood should cause an increase of 1 to 1.5 gm. per 100 c.c. in the hemoglobin of the recipient, and an increase in the erythrocytes of 400,000 to 450,000 per cubic millimeter.

Patients who have pernicious anemia seldom require transfused blood. Adequate treatment with liver generally will accomplish as much each week as would the transfusion of 500 c.c. of whole blood.

Hemolytic anemias constitute a group of diseases in which the transfusion of blood is hazardous and the results uncertain. In congenital hemolytic icterus, even though a crisis with rapidly increasing anemia exists, the transfusion of blood usually can be delayed until immediately after splenectomy. In acquired hemolytic anemia the results of splenectomy are not certain. If a toxic hemolytic agent, such as a sulfonamide, is known to be the cause, the agent should be withdrawn. After this has been done, it may be necessary to transfuse blood and this may be successful. When no toxic or congenital factor can be demonstrated, the greatest difficulty with the transfusion of blood will be encountered. Before or after splenectomy, blood must be given with utmost caution. The infusion of plasma probably is less dangerous than the infusion of whole blood.

In the presence of aplastic anemia the transfusion of whole blood is indicated. As is true in hemolytic anemias of unknown origin, all possible toxic substances should be withheld from the patient. Agranulocytosis is seldom benefited by transfused blood. In this disease we have had no experience with transfusion of the leukocyte layer of centrifuged blood, but we have not observed any benefit from the repeated transfusion of whole blood. In bone-marrow depressions

caused by toxic conditions such as renal or hepatic failure, the need of transfused blood may be great, but the results are not spectacular. The anemias associated with acute leukemia seldom will be more than very temporarily benefited. The same is often true of anemia associated with malignant processes, unless surgery is to be done. The relatives of patients who have hopeless conditions always should be made acquainted with the futility and the fleeting benefits of the transfusion of blood in such instances.

Infections of all types often are accompanied by anemia. Chronic loss of blood may be a factor, but the toxicity of the infection generally is the more important. Normal regeneration of blood does not take place, and deficiency of iron is not often important. For this reason, iron is not of much value. The first consideration in treatment is eradication of the infection. Whole blood may be a valuable adjunct with which to combat the anemia, and perhaps in some infections it is of some immunologic value. The patient who has an infection is more likely to experience a pyrogenic reaction to the transfusion of blood than are other patients. There may be some added value in repeated small quantities (200 to 250 c c) of transfused blood when anemia is not severe. In diseases such as chronic ulcerative colitis, periarteritis nodosa and disseminated lupus erythematosus, which may be questionably classified with the infectious processes, the transfusion of blood often is of benefit but is accompanied by a high rate of reactions.

Diseases associated with tendencies toward hemorrhage often require transfused blood. In hemophilia there is evidence to suggest that a globulin fraction may contain a specific antihemophilic substance. Whole blood, however, generally is necessary when the bleeding process is active. In thrombocytopenic purpura, fresh whole blood combats the anemia and furnishes platelets, although the specific platelet effect is difficult to evaluate. In hemorrhages caused by deficiency of prothrombin, either natural or induced by anticoagulants, fresh whole blood is of value. Massive doses of vitamin K may correct the deficiency of prothrombin very rapidly, however, if hepatic function is normal. Whole blood or plasma is not administered for its prothrombin content, but to replace loss of blood.

At the Clinic, the transfusion of whole blood has been most widely used among patients preoperatively and postoperatively. No definite rules can be established regarding the need for preoperative transfusion. In general, if any major procedure is to be carried out and the value for hemoglobin is less than 8 or 9 gm per 100 c c of blood or the erythrocyte count is less than 3,500,000 per cubic millimeter, whole blood is transfused. If the operation involves any unusual loss of blood or extensive trauma to tissue, whole blood is used during or soon after surgery. The amount of blood lost at surgery may be great, and it is

sometimes necessary to use several liters of whole blood. If trauma or low blood pressure is more significant than loss of blood, then plasma, serum albumin or solution of gelatin may be used.

Extensive and rapid loss of blood is most often encountered outside the operative room in bleeding gastro-intestinal lesions and in obstetric emergencies. Adequate amounts of whole blood are essential, and the danger of increased bleeding from an inaccessible lesion is not a contraindication to the transfusion of such blood. In acute loss of blood it is essential to maintain an adequate blood volume and number of circulating erythrocytes.

In some conditions, such as trauma and burns, shock without much loss of blood from the vascular system may occur. In these instances plasma, serum albumin, or perhaps solutions of gelatin or acacia may be used to restore volume. Although plasma at present is universally available and will continue to be available, whole blood still is most easily obtained and is useful, since some degree of anemia usually develops, especially in the presence of burns. The rule that each 10 per cent of body surface burned will require 1,000 c c of blood or plasma may be followed with considerable success.

In many patients, hypoproteinemia will require treatment. At present, blood offers the most effective treatment for maintenance of a patient until an emergency has passed, although it leaves much to be desired. Although plasma, serum albumin and solutions of acacia or gelatin may aid in combating the edema associated with hypoproteinemia, blood and an adequate intake of protein are more effective in restoration of serum proteins. All too frequently, an underlying disease such as nephritis makes such procedures futile.

The most commonly encountered type of poisoning in which the transfusion of whole blood or suspended erythrocytes is of value is carbon monoxide. We have had no experience with the so-called exsanguination-transfusion technic among such patients.

There are relatively few contraindications to the transfusion of blood which have not already been mentioned in the consideration of the dangers of transfusion. When circulatory failure is present or imminent, great caution must be used and the material must be transfused slowly. If either plasma or erythrocytes alone are indicated, the volume need be only half, or less, as great as that of whole blood.

CLINICS ON OTHER SUBJECTS

RADIOPHOSPHORUS IN THE TREATMENT OF BLOOD DYSCRASIAS

BYRON E. HALL AND CHARLES H. WATKINS

IN the short space of thirteen years, important developments in the field of nuclear physics have been applied with startling rapidity to researches in biology and medicine. In 1934, Joliot and Curie, son-in-law and daughter of Pierre and Marie Curie, demonstrated that radioactivity could be artificially induced in various elements. Shortly thereafter, the development of the cyclotron was announced by E. O. Lawrence and Cooksey. The significance of Lawrence and Cooksey's discovery has been manifested by the fact that artificial radioactivity of all chemical elements may be produced in quantity in the cyclotron.

Radioactive isotopes emit rays similar to those from radium, yet they retain the chemical properties of stable elements. Exact quantitative measurements of radioactive tagged elements can be made with the aid of a Geiger counter, and hence, a new method, the isotope-tracer technic, has been developed for investigating complex physiologic and metabolic problems in health and disease. The importance of the development of the isotope-tracer technic, comparable perhaps to the discovery of the x-rays by Roentgen, should be emphasized, for this method has been found to be of the greatest value in elucidating fundamental problems of normal and pathologic physiology.

Knowledge of emission of rays by radioactive elements similar to those of radium has led during the last decade to an investigation of the possible therapeutic effectiveness of certain isotopes in various diseases. Tracer doses of isotopes are small and are insufficient to cause significant changes in the metabolism of cells in which they are retained. Therapeutic doses must be sufficiently large to alter cellular metabolism. The choice of the radioactive isotope to employ in the treatment of a given disease depends on the physical and chemical properties of the element. The half-life of the isotope, the type of ray or rays emitted, the depth of penetration of the rays in tissues and the chemical behavior and distribution of the element in the body are of particular significance.

Because of the tendency to localization selectively in certain tissues, a few radioactive elements have been subjected to therapeutic trial. These are radio-iodine, radiostrontium and radiophosphorus. The first of these, radio-iodine, is concentrated almost exclusively in the thyroid gland and has been utilized with encouraging results in the treatment of Graves' disease and in some cases of carcinoma of the thyroid gland. Radiostrontium, as well as radiocalcium, is localized more or less exclusively in bone, and has been employed as a therapeutic agent in neoplastic diseases of this tissue. The therapeutic efficacy of radiostrontium, however, has been found to be in no way superior to that of other forms of radiation therapy. The third element, radiophosphorus, when introduced into the living organism, enters into all phases of phosphorus metabolism. It is concentrated primarily in bone and bone marrow but relatively large amounts also are localized in the liver, spleen and lymph nodes. After initial experimental studies, J. H. Lawrence and his associates²³ in 1939 advocated that radioactive phosphorus be employed as a therapeutic agent in leukemia in a wide variety of disorders of the hematopoietic system, particularly in malignant neoplastic diseases, has been investigated by a number of workers. We have studied the effect of radiophosphorus as a therapeutic agent since 1941. However, before recounting our experiences with this form of therapy, it would seem advisable to review briefly certain important physical and chemical properties of this substance and to outline the course of events that follows its introduction into the living organism.

DEFINITION OF MILLICURIE AND PHYSICAL PROPERTIES OF RADIOPHOSPHORUS

The dosage of radiophosphorus is measured in terms of millicuries. One millicurie (mc) is that amount of radioactive substance of which 37,000,000 atoms disintegrate per second. A microcurie (μc) is 0.001 millicurie.

The rapidity of decay of any radioactive substance is expressed by the time required for half of any initial stock of atoms to disintegrate. This is called the "half-life" of the isotope. In the case of radiophosphorus, thirty-five out of every million atoms undergo spontaneous transformation to stable sulfur each minute, giving radioactive phosphorus a half-life of 143 days.

In contrast to radium which emits alpha, beta and gamma rays, radiophosphorus emits only the electron alpha or beta ray. The beta particle is emitted the moment radiophosphorus is transformed into stable sulfur. The depth of penetration of the beta ray varies in different tissues, the maximal range of penetration is approximately 7

mm.²⁰ The beta ray has the capacity to produce ionization in tissues, and therefore its radiation effects are basically similar to those of roentgen rays and of radium

DISTRIBUTION IN NORMAL AND PATHOLOGIC TISSUES

Radiophosphorus is chemically indistinguishable from ordinary stable phosphorus and, therefore, enters into all phases of phosphorus metabolism in the same manner as does the natural element. After administration it is rapidly and selectively withdrawn from the blood by certain tissues and cells. According to Reinhard and his co-workers the selective uptake of phosphorus by cells is dependent principally on three factors: (1) the total amount of phosphorus in exchangeable form in the tissue, (2) the rate of turnover of phosphorus by the tissue, and (3) the rate at which new tissue is formed.

As stated previously, in normal animals radiophosphorus is deposited in large amounts in bone and bone marrow, and in somewhat smaller quantities in liver, spleen and lymph nodes. Under pathologic conditions, the uptake has been found to be much higher in rapidly metabolizing neoplastic tissues than it is in the same type of tissue in a normal state of growth.

In leukemia and in polycythemia the isotope is taken up rapidly by both circulating erythrocytes and leukocytes during the first twenty-four hours after administration.^{8, 9, 10, 28} The concentration in erythrocytes then falls sharply, while the concentration in leukocytes falls more slowly and the radiophosphorus is retained for much longer periods and in greater quantities than in the erythrocytes.

In certain diseases of the hematopoietic system the distribution of radiophosphorus in various organs and tissues has received considerable attention.^{2, 3, 5, 10, 18, 20, 27, 30} The studies of Reinhard and his associates were especially illuminating in this regard. In chronic myelogenous leukemia greater activity was found in the bone marrow than in any other organ, whereas in chronic lymphatic leukemia the liver, spleen and lymph nodes in most instances contained a higher concentration of radiophosphorus than did the bone marrow. In acute leukemia or leukosarcoma variable results were observed, but in general, more of the material accumulated in the liver and spleen than in the bone marrow. In most cases, however, the concentration of radiophosphorus was found to be lower in lymph nodes than in bone marrow, liver, spleen or kidney. In lymphosarcoma and actively progressing Hodgkin's disease Erf and Lawrence⁷ found as great a retention of radiophosphorus in lymph nodes as in the liver and kidney. However, in one case of Hodgkin's disease in which the lymph nodes had become densely fibrotic, the uptake of radiophosphorus was less than in the other tissues assayed.

Data concerning the differential uptake of radiophosphorus in various organs in other diseases also have been accumulated. These diseases include melanoma and melanosa sarcoma, seminoma, neuroblastoma, Ewing's sarcoma, fibrosarcoma, reticulum cell sarcoma, multiple myeloma and metastatic carcinoma. In general, the distribution of the substance among different organs and tissues of the body depends on the type of neoplastic disease present, the degree of infiltration of an organ with abnormal cells and the rate of growth of these cells. Tissues having a high concentration and a rapid turnover of stable phosphorus also take up higher concentrations of radiophosphorus than do normal tissues.

ABSORPTION AND EXCRETION OF RADIOPHOSPHORUS

Radiophosphorus may be administered to patients either orally or intravenously. When the oral route is employed, from 15 to 50 per cent of the amount administered is excreted in the urine and feces during the first six days^{9, 20}. Most of this loss is due to a lack of absorption in the gastro-intestinal tract. As a general rule, it is safe to assume that 25 per cent of the amount of radiophosphorus administered orally will be lost in the stool and that 75 per cent will be absorbed.

When radiophosphorus is administered intravenously to normal subjects, from 25 to 50 per cent of the quantity injected is excreted during the first six days. In leukemic and polycythemic patients the excretion of the isotope is less than that in normal individuals, varying from 5 to 25 per cent of the amount injected over a similar period of time^{9, 20}. With the intravenous route of administration most of the loss occurs in the urine.

MATERIAL AND METHODS

Our studies of treatment with radiophosphorus began in the fall of 1941. The isotope was obtained during the first three years of work from the University of California through the courtesy of Dr. J. H. Lawrence and during the last one and a half years from the Massachusetts Institute of Technology through the courtesy of Dr. Robley Evans. It was supplied as an isotonic solution of dibasic sodium phosphate, containing 15 mg of the salt per cubic centimeter of solution. On receipt, isotonic saline solution was added so that the specific activity of 1 cc was 1 mc. The material then was autoclaved for one hour in a rubber-stoppered vaccine bottle at a temperature of 250° F (121.1° C) and a pressure of 50 pounds (22.7 kg). The intravenous route of administration was utilized in all cases because studies have shown that thereby a more accurate relationship can be maintained between the amount retained and the dose administered than is possible with the oral route²⁰. For oral administration sterilization is not

required, but the material should be stored in the icebox to prevent the formation of mold

In order to calculate the correct dose to be administered to a patient, the physician must know the rate of decay of the isotope. The rate of

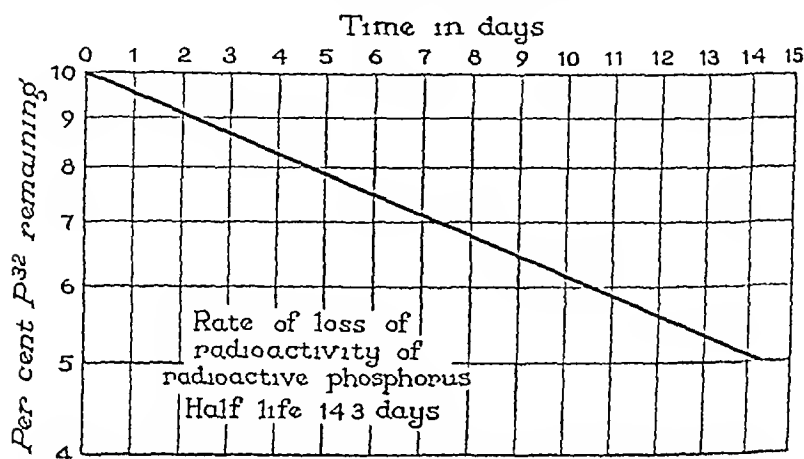


Fig 128 -Rate of loss of radioactivity of radiophosphorus (half-life 14.3 days)

TABLE 1
PATIENTS TREATED WITH RADIOPHOSPHORUS
TO APRIL 1, 1946

Disease		Cases
Polycythemia vera		97
Myeloma		22
Myelogenous leukemia (17 cases)	Chronic	15
	Acute	2
Lymphatic leukemia, chronic		3
Monocytic leukemia (2 cases)	Chronic	1
	Subacute	1
Hodgkin's disease of bone marrow		2
Total		143

loss of radioactivity follows a constant pattern that can be plotted on logarithmic paper as a straight line (fig 128). The specific activity per cubic centimeter of solution then can be read directly from the

chart at any given time after the initial determination of potency. For example, a specimen containing 1,000 microcuries of radiophosphorus per cubic centimeter of solution will have a specific activity of 950 microcuries per cubic centimeter at the end of twenty-four hours, 908 microcuries at forty-eight hours, 864 microcuries at seventy-two hours, and so on. It thus becomes a simple matter to translate specific activity into cubic centimeters of solution for any dose of radiophosphorus.

Throughout this investigation we intentionally restricted the use of radiophosphorus as a therapeutic agent to diseases in which the bone marrow was involved primarily by a pathologic process, or to diseases in which the marrow was extensively involved even though the primary site of the disease was in other organs. One hundred and forty-three patients have been treated (table 1).

POLYCYTHEMIA VERA

Prior to 1946 forty-eight cases of polycythemia vera in which radiophosphorus was used in treatment had been reported in the literature^{6, 13, 14, 21, 24, 31}. By October, 1946, the number of patients treated with radiophosphorus at various institutions in this country totaled 214 according to Erf.⁴ In addition to the thirty-eight patients from the Mayo Clinic included in Erf's data, fifty-nine patients have been treated which brings the total treated in this country to 273.

Of the ninety-seven patients who had polycythemia vera and who have been treated with radiophosphorus at this institution, fifty-four have been followed from nine months to four and a half years. The data to be presented are based on these fifty-four patients. The remaining forty-three patients were treated during the nine months prior to the writing of this paper, hence data concerning them are not included because it is felt that insufficient time has elapsed to permit subjecting the data to critical analysis.

Thirty-three of the fifty-four patients were men and twenty-one were women. They ranged in age from twenty-five to seventy-eight years. In thirty-two cases, the diagnosis of polycythemia vera had been made months or years previously and each patient had been treated by other means (venesection, oral administration of phenylhydrazine or roentgen irradiation). Five of these thirty-two patients had received courses of roentgen-ray treatment over the bones and bone marrow and one had received such treatment over the spleen. However, the polycythemia was under adequate control in only two of the thirty-two cases at the time the patients were admitted for treatment with radiophosphorus. In both cases, phenylhydrazine and venesection had been employed to control the disease, roentgen irradiation had not been given. In the remaining twenty-two of the fifty-four cases, the

- Penicillin, dermatitis from, *Jan*, 37, 38
 fever, urticaria and migratory poly-
 arthritis due to, *Jan*, 38
 in atypical pneumonia, *Jan.*, 57
 in bronchopneumonia, *Jan.*, 57
 in diphtheria, *Jan*, 62
 in lupus erythematoses, *Jan*, 211
 in meningococcal meningitis, *Jan.*, 76
 in pneumococcal meningitis, *Jan*, 71
 in pneumoma, *Jan*, 21, 54
 in prevention of postembolic pul-
 monary infection, *Jan*, 24
 in scarlet fever, *Jan*, 63
 in streptococcal meningitis, *Jan*, 79
 in subacute bacterial endocarditis,
Jan, 19
 reactions to, adverse, *Jan*, 81
 Pentosuria, *March*, 316, 318, 322
 Peptic ulcer, *Jan*, 101
 acid neutralization, *Jan*, 108
 parenteral therapy, *Jan.*, 111
 psychosomatic approach, *Jan*, 111
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 Phenobarbital in hypertension, *Jan*,
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 Phosphorus, radioactive, in treatment of
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 hemopoietic system, *Jan.*, 3
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 Friedländer's bacillus, *Jan*, 59
 penicillin in, *Jan.*, 21, 54
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 2 1 mixture, *March*, 335, 338,
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Jan, 47
 QUINIDINE in coronary thrombosis, *Jan*,
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 Quinine in lupus erythematoses, *Jan*,
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 poietic system, *Jan*, 3
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 Rest in coronary thrombosis, *Jan*, 158,
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 Rh factor, *Jan*, 236
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 Rhinitis, vasomotor, benadryl in, *Jan*,
 46, 49
 pyribenzamine in, *Jan*, 49
 Rutin in nephrosis, *Jan*, 141
 SALICYLATES in rheumatic fever, *Jan.*,
 99

diagnosis of polycythemia vera had not been made prior to the patients' admission to the Clinic

Considerable care was taken to exclude from the series cases of erythrocytosis secondary to anoxemia (emphysema, pulmonary fibrosis, pulmonary arteriosclerosis, congenital heart disease and so forth) and to other causes, such as brain tumor. In questionable cases, studies of the oxygen saturation and oxygen content of arterial blood were

TABLE 2
EFFECTS OF TREATMENT WITH RADIOPHOSPHORUS ON SYMPTOMS
IN FIFTY-FOUR CASES OF POLYCYTHEMIA VERA

Symptoms	Occur ence, times	Results					
		Complete Relief		Improved		No Improvement	
		Num- ber	Per cent	Num- ber	Per cent	Num- ber	Per cent
Fatigue	34	24	71	9	26	1*	3
Heat intolerance	20	17	85	3	15		
Dizziness	29	26	90	3	10		
Headache	27	22	81	5	19		
Blurring of vision	12	9	75	3	25		
Burning of conjunctivas, excessive lacrimation	4	4	100				
Pain in extremities	13	9	69	3	23	1†	8
Paresthesia	11	8	73	3	27		
Erythromelalgia	3	3	100				
Pruritus	6	2	33	2	33	2	33

* Superimposed thyrotoxicosis

† Endarteritis obliterans

made and treatment with radiophosphorus was not given in those cases in which anoxemia was found. In our experience the determination of the blood volume is an unreliable means of differentiating between the primary and secondary types of polycythemia, since we have observed increases in the volume of whole blood in several cases of secondary polycythemia as well as in polycythemia vera.

Results of Treatment.—Clinical Manifestations.—The degree of symptomatic improvement following treatment with radiophosphorus

is illustrated in table 2. The most striking improvement was noted in the group of symptoms attributable to increased blood volume, namely, headache, sense of fullness or pressure in the head, dizziness and visual disturbances. The degree of improvement, as a general rule, paralleled the reduction in blood volume and was greatest in those cases in which satisfactory hematologic remissions were induced. Failure to obtain complete relief of symptoms of this type was found to be due to a failure to induce satisfactory remissions.

Fatigue was a common symptom and was relieved completely in a comparatively high proportion of cases. When satisfactory hematologic remissions were obtained, it was common to hear the patient state that he had not felt so well in months or even years. One individual, however, continued to complain of marked fatigue after the induction of a satisfactory hematologic remission and subsequently was found to have exophthalmic goiter.

Intolerance to heat was a specific symptom in twenty cases and was relieved in a high proportion of cases. However, in several instances, this symptom recurred concomitantly with recurrence of the polycythemia.

The incidence of relief of pain or paresthesia in the extremities also was relatively good. An exception, in which the pain continued unabated despite adequate control of the polycythemia, occurred in an individual with endarteritis obliterans of the lower limbs.

Erythromelalgia was present in three cases, in all it was relieved completely when the polycythemia was brought under control. In one case the erythromelalgia developed a second time when the polycythemia recurred, but relief again was obtained with control of the polycythemia.

Pruritus was noted in six cases. In two, it was severe, and persisted unabated after the induction of satisfactory hematologic remissions. In the four remaining cases, it was less severe. In two of these four cases partial relief, and in two complete relief followed control of the polycythemia.

The incidence of reduction in the size of the spleen and liver during induced remissions also was relatively high. Adequate follow-up data were available in thirty of forty cases in which splenomegaly occurred. In these thirty cases, the spleen was reduced in size in twenty-seven. No reduction was noted in three cases, but in none of these three was a satisfactory hematologic remission induced.

The degree of reduction in the size of the spleen was extremely variable. In cases in which the spleen was only slightly enlarged, descending 2 to 3 cm. or less below the costal margin, control of the polycythemia often resulted in recession in size to a point where the organ no longer could be palpated below the costal margin. In cases in which splenomegaly of moderate degree occurred, treatment usu-

ally resulted in moderate and occasionally in marked reduction in the size of the organ. However, in cases in which the spleen was enormously enlarged, descending to the pelvic brim and below, the reduction in size usually was much less striking, probably as a result of fibrosis. Interestingly, in several cases in which a reduction in size of the spleen was noted after adequate control of the polycythemia, the spleen became enlarged with recurrence of the polycythemia and the associated increase in blood volume.

Follow-up data concerning changes in the size of the liver were adequate in twelve of seventeen cases in which hepatomegaly was noted. After treatment, a reduction in size was observed in eleven of the twelve cases. In the remaining case in which no significant

TABLE 3
EFFECT OF TREATMENT OF POLYCYTHEMIA VERA WITH
RADIOPHOSPHORUS ON ERYTHROCYTE COUNT

Erythrocytes, millions per cubic millimeter	Before Treatment		After Treatment*	
	Number	Per cent	Number	Per cent
Less than 5.0			34	63
5.0-5.4			13	24
5.5-5.9	7	13	1	2
6.0 or more	17	87	6	11
Total	54	100	54	100
Mean count	7,160,000		1,560,000	

* Lowest count recorded

change in the size of the liver occurred, a satisfactory hematologic remission was not induced.

Improvement in the degree of so-called ruddy cyanosis of the skin and mucous membranes, conjunctival congestion and distention of the retinal venules also was noted concomitantly with reduction in blood volume.

Hematologic Response—Varying degrees of improvement in the hematologic picture were noted in all cases in which radiophosphorus was used. The volume of packed erythrocytes per 100 cc. of blood (cell volume per cent or hematocrit reading) has been found to be a more accurate measurement of the erythrocyte mass than is the erythrocyte count, owing to the fact that microcytosis occurs more com-

monly than normocytosis in polycythemia vera. In individuals whose erythrocytes number in the neighborhood of 6,000,000 cells per cubic millimeter, not infrequently a normal cell volume per cent is obtained. Consequently, it is felt that data pertaining to cell volume per cent are of greater significance than data based on erythrocyte counts. The degrees of reduction in erythrocyte counts and cell volume per cent following treatment with radiophosphorus are shown in tables 3 and 4. Reduction in amount of hemoglobin paralleled the drop in number of erythrocytes.

Patients whose cell volume per cent fell to less than 55 and whose erythrocytes decreased in number to less than 5,500,000 per cubic millimeter were found to be relieved of those symptoms generally

TABLE 4

EFFECT OF TREATMENT OF POLYCYTHEMIA VERA WITH RADIOPHOSPHORUS
ON VOLUME OF ERYTHROCYTES

Cell Volume, per cent (hematocrit reading)	Before Treatment		After Treatment*	
	Number	Per cent	Number	Per cent
Less than 50			35	73
50-54	1	2	8	17
55-59	4	7	4	8
60 or more	19	91	1	2
Total	54	100	48	100
Average cell volume, per cent	69		44	

* Lowest reading recorded.

attributed to increased blood volume, whereas patients in whom a fall in cell volume per cent and number of erythrocytes per cubic millimeter was not sufficient to give values of less than 55 for packed cells and 5,500,000 for erythrocytes, obtained partial but not complete relief of similar symptoms. Consequently, we have arbitrarily divided our cases into two groups: those in which satisfactory hematologic remissions were induced and those in which partial hematologic remissions were induced. Patients classified as having satisfactory hematologic remissions were those in which the cell volume per cent fell to less than 55 and the erythrocyte count to less than 5,500,000. The remaining patients, in whom the drop that occurred did not reach lower values than those just mentioned, were classified as having par-

tial hematologic remissions In the series of fifty-four cases, satisfactory hematologic remissions were observed in forty-four or 81.5 per cent and partial hematologic remissions in ten or 18.5 per cent

The observation that radiophosphorus in doses employed therapeutically in polycythemia vera profoundly affects not only erythrocytosis but also the formation of leukocytes and platelets in the marrow, previously had been noted^{14, 15, 26} This effect on the leukocyte count is illustrated in table 5 Prior to the institution of therapy, the average leukocyte count was 16,700 and the average platelet count was 277,000 per cubic millimeter After treatment the average minimal leukocyte

TABLE 5
EFFECT OF TREATMENT OF POLYCYTHEMIA VERA WITH RADIO-
PHOSPHORUS ON LEUKOCYTE COUNT

Leukocytes, thousands per cubic millimeter	Per cent of 54 Cases	
	Before Treatment	After Treatment*
30 or more	8	
25-29	4	
20-24	17	
15-19	20	2
10-14	31	4
5- 9	17	11
Less than 5	2	53
Mean count	16,700	5,500
Range	4,800-54,000	1,700-16,700

* Lowest count recorded

count was 5,500 per cubic millimeter, and the average minimal platelet count was 124,000 per cubic millimeter In cases in which leukopenia and thrombocytopenia developed, the numbers of leukocytes and platelets subsequently increased gradually in the course of several weeks but in most instances they did not return to pretreatment values during the period of the remission, however, with recurrence of the polycythemia, the number frequently increased to values higher than normal

It is of interest to note that two of the fifty-four patients had a moderately profound thrombocytopenia prior to treatment with radiophosphorus In one case, the platelet count was 92,000 per cubic milli-

meter prior to the institution of therapy Seven millicuries was administered and two months later 52 mc was given Two months after the second injection of radiophosphorus, the platelet count had fallen to 43,000 and petechiae were observed on the lower extremities Other phenomena of hemorrhage, however, did not occur A satisfactory remission, which lasted seven months, was obtained and during that time the platelet count gradually rose to the pretreatment value In the second case, the platelet count prior to treatment was 72,000 per cubic millimeter A dose of 35 mc of radiophosphorus was given and six weeks later 31 mc was administered At the time of the second injection, the platelet count was 43,000 but four weeks later it had risen to 91,000 Hemorrhagic phenomena did not develop A partial hematologic remission which lasted only three months was

TABLE 6
DURATION OF REMISSIONS AFTER TREATMENT OF POLYCYTHEMIA
VERA WITH RADIOPHOSPHORUS*†

Duration Remission, months	Number	Per cent
Less than 6	9	17
6-11	31	57
12-17	9	17
18-23	2	4
36-47	3	5
Total	54	100

* Time of inquiry, April 1, 1946

† In 54 of the 97 cases.

induced The failure to induce a satisfactory remission was attributed to the comparatively small dose of radiophosphorus administered. While no permanent harmful effects occurred in either patient, these cases serve to emphasize the risk of employing radiophosphorus in the treatment of polycythemia vera complicated by thrombocytopenia. In our opinion, patients of this type should not be treated with radiophosphorus but should be treated by other means

Duration of Remissions.—The fifty-four patients referred to in this communication have been followed from nine months to four and a half years Forty-two patients have been observed for a year or more Thirty-two patients are in remission at the time of writing so that accurate data concerning the length of the remissions induced with radiophosphorus cannot be given The duration of the remissions noted

up to the time of the last inquiry (April 1, 1946) is indicated in table 6 Three patients have had remissions which lasted three years or more, the longest being forty-seven months This patient still is in a remission One of the other two patients returned for a second course of treatment with radiophosphorus forty-four months after the first course had been given The remaining patient died at the age of seventy-five years, three years after treatment with radiophosphorus, the polycythemia had not recurred That the duration of the remission induced is not related to the length of time the patient has had the disease is indicated by the fact that the two patients who obtained remissions of forty-six and thirty-six months had been known to have polycythemia vera for eight and nine years, respectively, whereas a patient who had a remission of forty-four months was not aware of

TABLE 7

COMPLICATIONS OF TREATMENT OF POLYCYTHEMIA VERA
WITH RADIOPHOSPHORUS*

	Cases		Lowest Value Recorded
	Number	Per cent†	
Thrombocytopenia (less than 100,000)	21	39	22,000
Leukopenia (less than 5,000)	29	54	1,700
Anemia (less than 4,000,000)	10	18	3,010,000

* In 54 of the 97 cases

† Total is more than 100 per cent because some patients suffered from more than one complication.

the nature of his illness until three months prior to treatment with radiophosphorus

Fifteen of the fifty-four patients have had two courses of treatment with radiophosphorus, and six of the fifteen have had three courses of treatment. Fifty-one of the fifty-four patients are living In addition to a patient who died of congestive heart failure, one patient died, eighteen months after treatment with radiophosphorus, of acute leukopenic myelogenous leukemia This case has been reported in detail previously¹⁴ The remaining patient died, one year after the institution of therapy, of subacute monocytic leukemia of the Naegeli type

Complications—The complications that have been encountered with this form of treatment are largely hematologic, in the form of thrombocytopenia, leukopenia and anemia¹⁵⁻¹⁷ The frequency of oc-

currence of each of these complications in our series of cases is given in table 7. Any one of the complications was found to occur singly or in combination with either of the others, but in only one case were thrombocytopenia, leukopenia and anemia observed to develop simultaneously.

TABLE 8

LEUKOPENIA FOLLOWING TREATMENT OF POLYCYTHEMIA
VERA WITH RADIOPHOSPHORUS*

Leukocytes, thousands per cubic millimeter	Cases	
	Number	Per cent
10-49	16	30
30-39	7	13
20-29	5	9
Less than 20	1	2

* In 54 of the 97 cases

TABLE 9

TREATMENT OF POLYCYTHEMIA VERA WITH RADIOPHOSPHORUS
EFFECT ON PLATELET COUNT*

Blood Platelets, thousands per cubic millimeter	Per cent of 45 Cases	
	Before Treatment	After Treatment†
100-150	15.5	40.0
50-99	4.4	33.3
Less than 50		13.3
Mean count	277,000	121,000
Range	72,000-960,000	22,000-343,000

* In 45 of the 97 cases.

† Lowest count recorded

Considerable variation occurred in the time which elapsed between the administration of the isotope and the development of the complication. Leukopenia developed in from two weeks to six months after injection of radiophosphorus, thrombocytopenia in from three weeks to two months and anemia in from two to ten months. The degree of leukopenia encountered is given in table 8. The leukopenia and anemia were of relatively short duration and no other complications

were noted to result from their development. Thrombocytopenia, when it developed, tended to last somewhat longer than leukopenia or anemia and extended over periods of four to eight weeks. The degree of thrombocytopenia observed is shown in table 9. The only phenomenon of hemorrhage observed was the development of petechiae on the lower extremities in two cases. The petechiae eventually disappeared as the platelet counts rose.

In the early stage of this investigation the development of leukopenia, anemia and particularly thrombocytopenia was viewed with great concern, but as experience was gained in the estimation of the proper dose of radiophosphorus to be administered to any given patient, the frequency of occurrence of hematologic complications was reduced materially. Since phenomena of thrombosis are relatively common in cases of uncontrolled or partially controlled polycythemia vera, a moderate reduction in the number of blood platelets following treatment with radiophosphorus tends to protect the patient from this complication. At this writing, only one of the fifty-four patients in our series has experienced thrombosis after treatment with radiophosphorus, and in this instance the polycythemia was inadequately controlled.

Toxic reactions were not observed after injection of radiophosphorus, and radiation sickness did not occur in this group of cases. In no instance in our series has treatment with radiophosphorus resulted in the development of primary tumors of the bones or bone marrow, nor have complications of this type been reported from other institutions so far as we are aware. The danger of the development of osteogenic sarcoma is minimized by the fact that radiophosphorus is a short-lived isotope (half-life, 14.3 days) that emits only beta rays. In studies on animals the use of long-lived isotopes which emit alpha or gamma rays is required to produce bone tumors. It is obvious, however, that prolonged observation, for ten to fifteen years, or more, of patients receiving treatment with radiophosphorus will be necessary before any conclusions concerning this point can be drawn.

Details of Treatment—To affect erythropoiesis adversely, relatively large doses of radiophosphorus are required. Lawrence and his associates^{21, 24} advocated an initial dose of from 5 to 7 mc, followed by subsequent injections of similar amounts at intervals of three to four weeks. However, in our experience, as well as in that of Reinhard and his co-workers, an interval of from six weeks to three months between injections of radiophosphorus is preferable to the shorter period suggested by Lawrence and his associates. Mature erythrocytes circulate for ninety to 120 days, so that even though erythropoiesis in the marrow is reduced immediately after an injection of radiophosphorus, a latent period of three to six weeks or more occurs before a significant decrease in the erythrocyte count in the peripheral blood stream is

noted²⁶ A second injection of radiophosphorus given three or four weeks after the first may not only be unnecessary but may result in overtreatment. Twenty of our fifty-four patients obtained satisfactory hematologic remissions from one injection of the substance

Because of the existence of a latent period in the decrease of the erythrocyte count after an injection of radiophosphorus, we have followed the procedure of performing venesection prior to the administration of the isotope in order to minimize the danger of complications, particularly the development of phenomena of thrombosis. Complications of this type are comparatively common in cases of severe uncontrolled polycythemia and conceivably could occur as readily during the latent period as before administration of the substance. In general, the procedure we have employed in the treatment of patients who have polycythemia vera is as follows. Patients who had not had treatment of any type previously and in whom the polycythemia vera was uncontrolled, and patients who had had treatment previously but in whom the disease was either uncontrolled or under only partial control underwent repeated venesection, performed daily or every second day until the cell volume per cent fell to decidedly lower values, usually to less than 55. One injection of 3 to 7 mc of radiophosphorus then was administered and the patient was dismissed with the request that he return in six to eight weeks for re-examination. At the time of the second visit, a second injection of radiophosphorus was administered to all patients in whom satisfactory hematologic remissions had not been obtained except in those cases in which complications in the form of leukopenia or thrombocytopenia had developed. If either of the latter complications was present, the patient was kept under observation until the leukocyte and blood platelet counts had returned to normal before the second, smaller injection of radiophosphorus was administered.

Patients with polycythemia who had been under treatment and in whom the polycythemia was under adequate control were not bled prior to the administration of the isotope. After the first injection of radiophosphorus they were handled in a manner identical to that used for the two groups mentioned in the previous paragraph.

At the beginning of this investigation, an attempt was made to calculate the size of the dose of radiophosphorus to be administered on the basis of the body weight of the individual. This procedure seemed advisable from a theoretical standpoint. However, in practice it was learned that this plan was inadequate owing to the wide variations in the clinical severity of the disease. For example, doses of from 50 to 100 microcuries per kilogram of body weight induced satisfactory hematologic remissions in thirteen patients with apparently mild forms of the disease, whereas doses of 240 microcuries per kilogram of body weight resulted only in partial remissions in two

patients with severe polycythemia. It was then found that doses based on the apparent clinical severity of the disease as well as on body weight gave better results than were obtained with doses based on body weight alone. The clinical severity of the disease was estimated by the degree of polycythemia present at the time the original diagnosis was made, the severity of the symptoms, history of complications, particularly phenomena of thrombosis, and the ease or difficulty with which the condition was controlled in patients who had been treated by other means.

The total dose and number of injections required to induce remissions varied from patient to patient. These are given in table 10. One

TABLE 10
DOSE AND NUMBER OF INJECTIONS OF RADIOPHOSPHORUS
IN TREATMENT OF POLYCYTHEMIA VERA*

Number of Injections	Cases	Dose, mc	Remission		
			Longest Duration, months	Satisfactory	Partial
1	20	3.0-7.9	18+	20	
2	25	5.0-14.0	45+	20	5
3	8	11.0-18.4	12	5	3
4	1	21.8	3+		1

* In 54 of the 97 cases

patient who was given one injection of 4,000 microcuries, or 55.5 microcuries per kilogram of body weight, obtained a satisfactory hematologic remission which lasted eighteen months, whereas a patient who received four injections totaling 21,800 microcuries, or 263 microcuries per kilogram of body weight, obtained only a partial remission. It is interesting to note that eight of the nine patients in whom partial remissions were induced received doses of from 11.5 to 21.8 mc while thirty-seven of forty-five patients who obtained satisfactory remissions received less than 11.5 mc. The factor or factors governing the response of patients to this type of therapy are as yet unknown, and hence, treatment must be individualized to a high degree.

The largest total quantity of radiophosphorus administered to any individual in our series was 38 mc. This quantity was given in three courses over a period of four years.

LEUKEMIA AND ALLIED DISEASES

The administration of radiophosphorus in leukemia and allied diseases differs from that in polycythemia vera. An attempt is made to minimize the effect of the isotope on the formation of erythrocytes and blood platelets while obtaining at the same time a maximal effect on leukopoiesis. As Lawrence and his associates²³ have shown, this can best be accomplished by administering radiophosphorus twice a

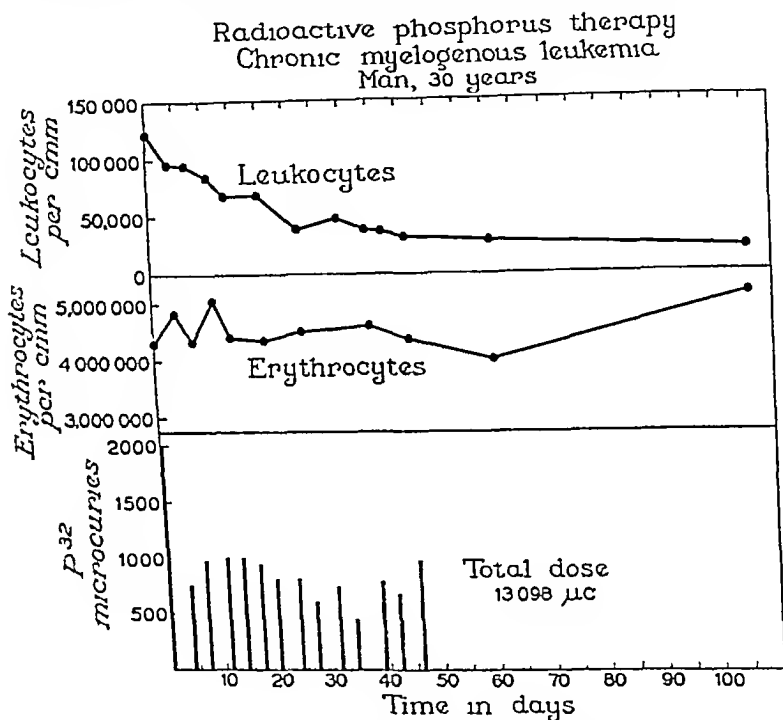


Fig 129—Chronic myelogenous leukemia Man, 30 years of age. One month previously, patient hospitalized with an acute febrile illness diagnosed as pneumonia. Leukemia discovered on routine examination of the blood. No symptoms of leukemia prior to the administration of radiophosphorus. The remission induced by therapy with radiophosphorus lasted five months.

week until the desired effect is obtained. An initial dose of from 1 to 3 mc. usually is given. Thereafter, the size of the biweekly injections varies from 0.5 to 20 mc.

Chronic Myelogenous Leukemia—Reports on the use of radiophosphorus as a therapeutic agent in 121 patients with chronic myelogenous leukemia have been published.^{1, 11, 13, 18, 23, 25} To this number of 121 patients, we have added fifteen. Seven of the fifteen patients had had courses of treatment with roentgen rays prior to the

administration of the isotope, and eight had had no irradiation of any kind. Nine were women and six were men. They ranged in age from fourteen to sixty-six years.

Remissions which lasted from four to fourteen months were induced in the eight patients who had not had previous irradiation. The remissions were characterized by marked diminution in the leukocyte count (figs 129, 130 and 131), some reduction in the size of the spleen and symptomatic improvement. In five of the eight cases, anemia of moderate severity was present prior to the institution of treatment. In

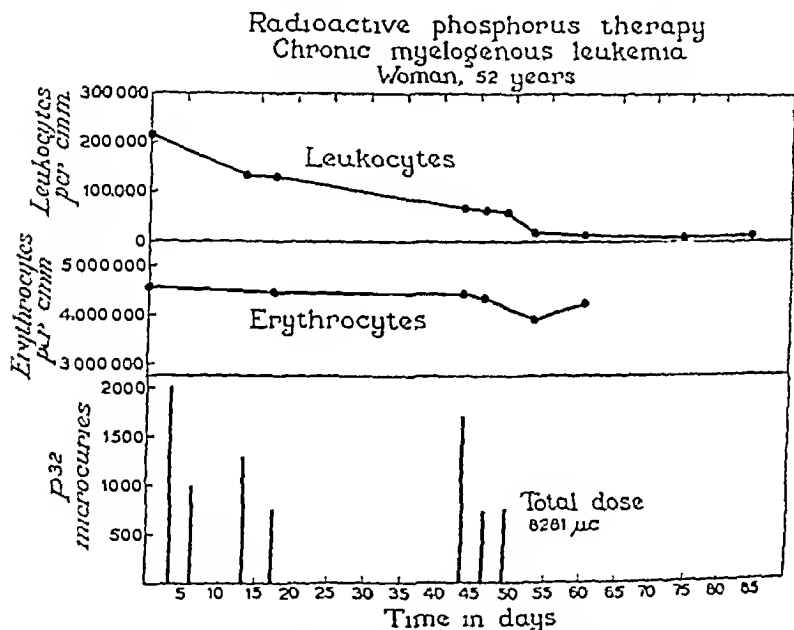


Fig 130—Chronic myelogenous leukemia. Woman, fifty-two years of age. Leukemia discovered at time of routine physical examination. No symptoms and no treatment prior to the administration of radiophosphorus. A remission was induced that lasted eighteen months.

all five cases, the erythrocyte counts returned to normal as the leukocyte counts fell (fig 131) during the course of treatment. It is known that the bone marrow in chronic myelogenous leukemia is markedly hyperplastic owing to the enormously increased regeneration of granulocytic elements. Erythropoiesis thereby is impaired, resulting in a myelophthisic type of anemia. Preliminary studies indicate that administration of radiophosphorus impairs leukopoiesis sufficiently to cause a marked drop in the leukocyte counts, probably through destruction of immature granulocytic elements. However, with the doses employed in this study, erythropoiesis is not inhibited and, as the

number of granulocytic cells in the marrow is reduced, normal erythropoiesis is resumed and the patient is relieved of anemia

Of the seven patients who had been treated with roentgen irradiation prior to the institution of therapy with radiophosphorus, one was in an early stage of the disease, four were in a moderately advanced stage and two were in a far-advanced stage. Remissions were induced in the cases of moderately advanced leukemia and were maintained

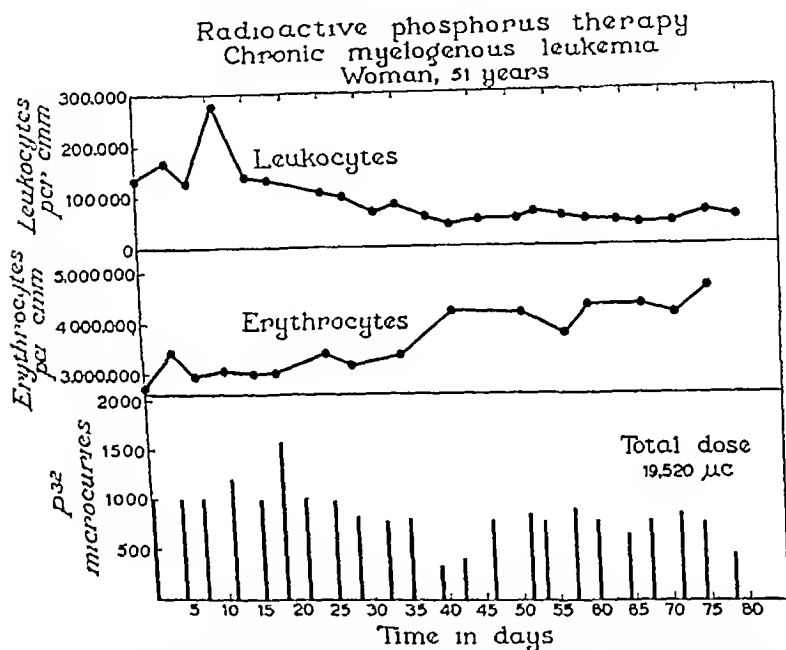


Fig 131—Chronic myelogenous leukemia. Woman, fifty-one years of age. Diagnosis of leukemia established two years previously. Three courses of roentgen therapy over the spleen administered over a period of eighteen months. Returned in critical condition. Treated with radiophosphorus over a period of eleven weeks. Note rise in erythrocyte count following the fall in the number of leukocytes in the peripheral blood. A much larger total dose of radiophosphorus was required to induce a satisfactory hematologic and clinical response in this person than in the patients whose hematologic data are shown in figures 129 and 130. The remission lasted four months

for many months by monthly or bimonthly injections of the isotope. In the cases of far-advanced leukemia, treatment resulted in transient improvement in one case but was ineffective in the other.

The smallest amount of radioactive material required to induce a remission in this series of fifteen cases was 55 mc. administered over a period of one month and the largest was 251 mc. given over a period of three and a half months. Thus, there is a wide range in the quantity of radioactive material needed to restore the leukocyte count

approximately to normal, and in leukemia, as in polycythemia vera, treatment with the isotope must be highly individualized.

Six of fifteen patients who had chronic myelogenous leukemia have died. The terminal blood picture was that of acute leukemia in each case. The first indication of a change in the severity of the disease was a failure of the leukocyte count to fall during treatment with radiophosphorus. In contrast to the steady drop that usually occurred during treatment, the counts became erratic and eventually a rise took place. Anemia then developed and examination of blood smears frequently revealed increased numbers of myeloblasts, leukoblasts and promyelocytes. Concomitant with these changes, patients complained of weakness, shortness of breath, night sweats, fever and pain in the left upper quadrant, associated usually with progressive enlargement of the spleen. The terminal picture was ushered in by a marked rise in the leukocyte count, a rapid fall in the number of erythrocytes and the appearance of enormous numbers of stem cells in the peripheral blood stream. However, it is interesting that even in the terminal stage, phenomena of hemorrhage were not observed in our cases.

While it is known that an acute leukemic phase not infrequently occurs as a terminal event in chronic myelogenous leukemia, many patients with this disease die from other causes, namely, intercurrent infections, severe anemia or phenomena of hemorrhage. Since all our patients who died had a terminal fulminating type of leukemia, the question whether treatment with radiophosphorus could have precipitated the acute phase has been raised. This question cannot be answered at the present time. Nevertheless, the answer to it ultimately must be obtained before therapy with radiophosphorus can be accepted as an effective method for inducing remissions in chronic myelogenous leukemia.

Chronic Lymphatic Leukemia—In chronic lymphatic leukemia we have employed roentgen irradiation in preference to treatment with radiophosphorus except in occasional cases in which sternal aspiration revealed extensive leukemic involvement of the bone marrow. It was felt that since the uptake of radiophosphorus had been found to be higher in the bone marrow than in lymph nodes, the administration of this isotope to patients having lymphatic leukemia not only would have little effect in reducing the lymphadenopathy but also might adversely affect the formation of erythrocytes, granulocytes and platelets in the bone marrow. However, Reinhard and his associates found therapy with radiophosphorus to be as satisfactory as, but no better than, treatment with roentgen rays. They observed a reduction in the size of lymph nodes and spleen after treatment with the isotope in thirty cases of chronic and subacute lymphatic leukemia, in some cases the reduction in size did not occur until many months after

therapy was started. They also found that somewhat smaller doses of radiophosphorus sufficed to restore the total leukocyte count to normal in the lymphatic form of leukemia than were required in myelogenous leukemia. The results of treatment with radiophosphorus in ninety-five cases of chronic and subacute lymphatic leukemia have been published.^{1, 11, 12, 13, 18, 21, 23, 24, 26, 29, 31}

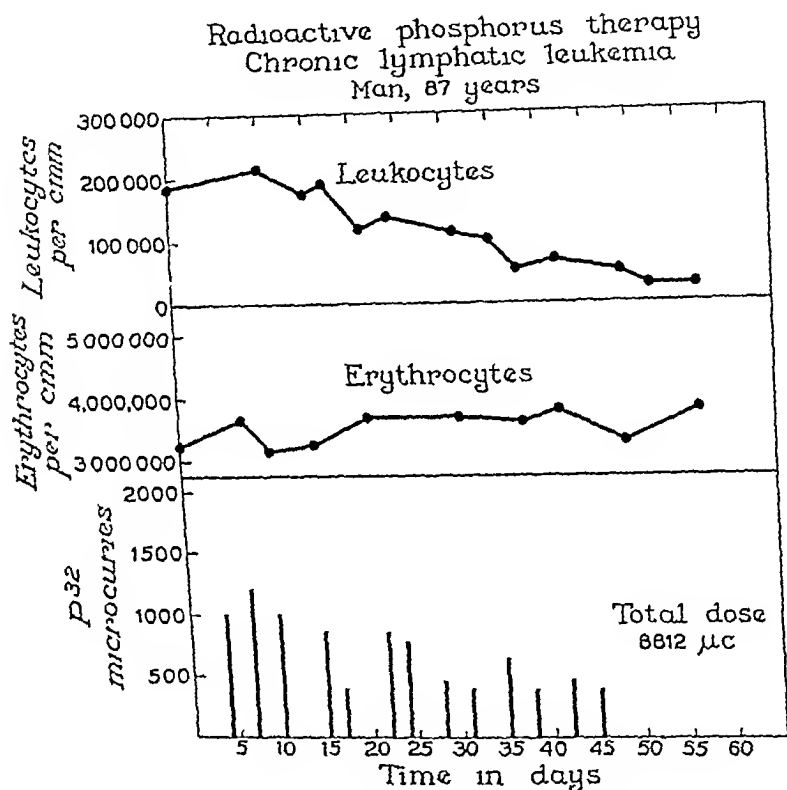


Fig 132—Chronic lymphatic leukemia. Man, eighty-seven years of age. Patient admitted with an impacted intertrochanteric fracture of the left femur. Examination revealed chronic lymphatic leukemia in addition to the fracture. Treatment with radiophosphorus instituted because of the anemia associated with the high leukocyte value, despite the known benignancy of chronic lymphatic leukemia in the aged. This patient is in a remission twenty months after completion of therapy with radiophosphorus.

Contrary to our original supposition, our experience with radiophosphorus in three cases of chronic lymphatic leukemia closely parallels that of Reinhard and his associates. In each case the total leukocyte count fell approximately to normal (fig 132), symptomatic improvement occurred, and a moderate reduction in the size of the lymph

nodes and spleen was noted. The total dose of radiophosphorus administered to each patient varied from 80 to 122 mc. All three patients had slight to moderate anemia and one had thrombocytopenia prior to the institution of therapy. However, in no instance did treatment cause intensification of the anemia or the thrombocytopenia. All three patients are living and are having remissions at the time this is written, the longest remission has lasted fourteen months.

Acute Leukemia.—In acute leukemia of all types the results of treatment with radiophosphorus have been uniformly bad in the hands of all investigators^{1, 11, 18, 19, 22, 24, 26, 29, 31}. We feel, therefore, that radiophosphorus should not be employed in the treatment of this disease.

Multiple Myelomas.—The results of therapy with radiophosphorus in twenty-five patients with multiple myelomas or plasma-cell leukemia have been reported.^{11, 13, 18, 24, 26, 31} We have treated twenty-two patients, all of whom had myeloma. Sixteen were men and six were women. They ranged in age from thirty-seven to seventy-five years. The diagnosis of myeloma was verified in all cases either by sternal aspiration or by biopsy of a tumor.

The method of administration of radiophosphorus was essentially the same as that utilized in the treatment of leukemia, but in most instances smaller doses were employed. In fifteen of the twenty-two cases, radiophosphorus was given over periods ranging from four to eight weeks and the total dose administered varied from 36 to 120 mc. In seven cases treatment was interrupted by the development of complicating factors and was considered to be incomplete. In this group, the total dose administered varied from 21 to 65 mc.

Prior to the administration of radiophosphorus, anemia was noted in sixteen of the twenty-two cases, leukopenia in seven, and thrombocytopenia in six. In an attempt to minimize the effect of the isotope on the formation of erythrocytes, leukocytes and platelets in the marrow, radiophosphorus was given cautiously and in small doses. Despite these precautions, at the completion of treatment the anemia had become more profound in eleven cases, leukopenia was present in ten and thrombocytopenia was noted in seven.

In general, the results of treatment of myeloma with radiophosphorus have been discouraging. Treatment did not appear to affect the progressive course of the disease materially. Eight of the twenty-two patients are dead. Seven of the remaining fourteen patients have been re-examined at intervals after completion of therapy with radiophosphorus and each has shown clinical, roentgenologic and hematologic evidence of progression of the disease. On the other hand, ten of fourteen patients who were suffering from intense pain in the bones received varying degrees of relief during treatment, four patients obtained no relief whatsoever. However, an isolated observation

in one of our patients who had myeloma is, we believe, sufficiently interesting to warrant a detailed report

REPORT OF CASE—A white man, forty-four years old, a tailor by trade, first came to the Clinic in November, 1944, because of pain and swelling of his right ankle which had been present for eight months. In March, 1944, he had turned his right ankle. This was followed by swelling and pain which did not subside under treatment. A roentgenogram of the ankle was made and the patient was told he had a tumor of the bone. The swelling gradually increased in size and the pain

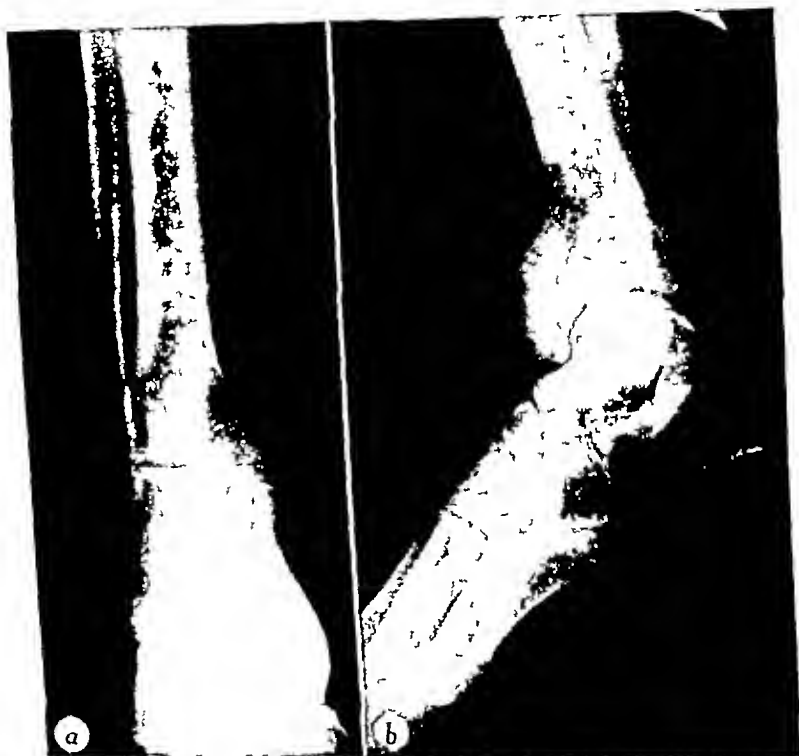


Fig 133—*a* and *b*, Myeloma of right ankle prior to treatment. Note destruction of internal malleolus of tibia and several small areas of destruction in fibula.

became more severe, so that the use of crutches was adopted. Shortly before admission to the Clinic, pain in the right shoulder also had been noted.

Examination of the ankle revealed a semifluctuant mass, 10 cm in diameter, which involved the internal malleolus. A roentgenogram of the ankle disclosed a destructive neoplasm which had obliterated the internal malleolus and had formed a large soft-tissue tumor (fig 133). Several rarefied areas in adjacent portions of the tibia and fibula also were noted. A roentgenogram of the thorax revealed a well-circumscribed oval mass, thought to be pleural in origin, located posterior to the axillary portion of the fourth rib on the left. Hyperproteinemia (97 gm. of protein per 100 c.c. of serum) with reversal of the albumin-globulin ratio (1:1.43)

and elevation of the sedimentation rate were noted but there was no Bence Jones proteinuria or anemia and a roentgenogram of the skull revealed nothing abnormal. Myeloma was suspected, but in order to exclude sarcoma with metastasis to the pleura, biopsy of the tumor of the ankle was performed. The pathologist reported "plasma cell myeloma."

A total of 107 me of radiophosphorus was given over a period of six weeks. However, not only did no reduction in the size of the tumor occur but also the biopsy wound failed to heal. Eventually tumor tissue appeared in the wound and bleeding developed. Local measures employed to stop the bleeding failed and active bleeding from rupture of a small artery occurred. In an effort to avoid



Fig 134—Myeloma of right ankle four months after completion of combined irradiation with radiophosphorus and roentgen rays. Note beginning of formation of new bone. No significant change in the lesions in the fibula. Second course of combined irradiation therapy given.

amputation, roentgen treatment over the tumor was undertaken by Dr W. C. Popp. After roentgen irradiation, gradual diminution in the size of the tumor occurred, the bleeding ceased, the biopsy wound healed and the patient was permitted to return to his home.

The patient returned in April, 1945, three months later, at which time all external evidence of the tumor of the ankle, except a scar at the site of removal of tissue for biopsy, had disappeared. He walked with a slight limp but had discarded his crutches. A roentgenogram of the ankle at that time showed evidence of formation of new bone (fig 134). However, the pain in his right shoulder had become more severe during the three months the patient had been at home and a roentgenogram disclosed almost complete destruction of the greater portion of the

acromion of the right scapula (fig 135) In view of the regression of the tumor of the ankle following use of the combined methods of irradiation, it was decided to repeat both procedures After the administration of 11.8 mc. of radiophosphorus over a period of six weeks, the right shoulder was irradiated with roentgen rays and the patient was dismissed

The patient returned a third time in October, 1945, because of pain in the left side of his chest He stated that he had experienced complete relief of pain in the right shoulder after completion of irradiation in June Roentgenograms of the right ankle and right shoulder in October revealed extensive formation of new bone not only at the site of the original tumor of the right tibia but also in the acromion of the right scapula (figs 136 and 137) On the other hand, roentgeno-



Fig. 135—Myeloma of right shoulder prior to treatment by combined irradiation
Note destruction of acromion.

grams of the chest showed multiple lesions which involved several ribs and the distal end of the left clavicle Since the patient was unable to remain for treatment with radiophosphorus, roentgen irradiation was administered over the ribs of the left side and once again he returned home

He returned for the fourth time in December, 1945, because of pain in his hands and legs and continued pain in his ribs Tumors in the region of the distal ends of both second metacarpal bones were present Roentgenograms of the ribs showed extensive destruction and absence of evidence of repair Roentgenograms of the hands and knees disclosed extensive involvement of the bones of the hands, fingers and knees Consequently, a third course of treatment with radiophosphorus

THE MEDICAL CLINICS

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SYMPOSIUM ON PEDIATRICS

FOREWORD

THE presentation of a symposium in a field of medicine as diversified as pediatrics permits a wide range of selection. There are so many subjects from which to choose that selective insertion in a single volume of limited size becomes as much a matter of subjective bias as objective discrimination. It is therefore inevitable that topics of equal and perhaps even greater pediatric interest have been omitted through inadvertence, by intention or by force of circumstances. These omissions are readily conceded. The special considerations which dictated the final choice of papers comprising this volume include the particular interests of the physician in practice, the presentation of contemporary knowledge and recent advances, diversification of subject matter, availability of authoritative contributors.

For maximal service to the practicing physician, it was deemed wise to give priority to articles of diagnostic and therapeutic import. This emphasis is indicated by the titles and content of the majority of the papers. The absence of review articles on chemotherapy (sulfonamides) and antibiotic therapy (penicillin and streptomycin) in childhood is explained by their abundance in the current pediatric literature. Nevertheless, health promotion and disease prevention are accorded proper attention and the nature, pathogenesis and prophylaxis of specific diseases are given appropriate space. The effort has been made to plan as comprehensive a coverage as possible and to effect a representative distribution of subjects. A similar effort has been made to secure contributors with high qualifications in their respective fields.

As Sponsor for this issue, I wish to thank the participants of this symposium for the time and effort expended in the preparation of manuscripts and the publishers for their enthusiastic cooperation in fostering the Pediatrics symposium which constitutes this New York number.

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New York, N. Y.

SAMUEL Z. LEVINE, M.D.



Fig 136—Myeloma of right ankle six months after second course of treatment by combined irradiation. Note degree of bone repair in the internal malleolus of the tibia. No significant change in the lesions of the lower fibula had occurred but involvement of the shaft of the tibia adjacent to the original tumor had developed.

was given. A total dose of 9.9 mc was administered over a period of four weeks and during this time the tumors of both metacarpal bones showed noticeable softening and regression in size. These changes were more pronounced in the left hand than in the right. Roentgen treatment then was given over the chest, hands and knees and at the time of dismissal the tumor of the left hand had disappeared and that of the right hand was markedly reduced in size.

We believe the observation of regression in the size of myelomatous tumors associated with formation of new bone after irradiation with radiophosphorus and roentgen rays is unique. The mechanism by which these changes were produced is not understood. Myelomatous tissue is known to be unusually resistant to roentgen irradiation.²³ In the case just described, the combined forms of therapy seemed to be more effective than either type of irradiation used alone. However, the fact should be emphasized that while combined irradiation caused regression of tumor growth locally in one case, the disease showed systemic signs of progression in all patients treated by this means.

Hodgkin's Disease.—Published reports have indicated that therapy with radiophosphorus is inferior to roentgen irradiation in the treatment of Hodgkin's disease.^{17, 18, 24, 25, 31} We have treated two patients who had Hodgkin's disease, in these cases sternal biopsy revealed extensive involvement of the bone marrow. Treatment resulted



Fig 137—Myeloma of right shoulder six months after treatment by combined irradiation. Note degree of bone repair in the acromion.

in intensification of the anemia, leukopenia and thrombocytopenia without materially affecting the course of the disease. Therefore, our experience is in line with that of other investigators—that roentgen therapy is the treatment of choice in this disease.

SUMMARY AND COMMENT

Radiophosphorus, employed in the treatment of various diseases of the bone marrow, was found to be most effective in polycythemia vera. Treatment with this substance was in no way curative, but resulted in the induction of remissions in a high proportion of cases. In our series of cases, the duration of the induced remissions varied from five months to nearly four years. In our experience polycythemia vera can be controlled more readily with internal irradiation than with any other therapeutic procedure now available and, therefore, it is felt that therapy with radiophosphorus is superior to other forms of treatment employed in the past.

In the chronic types of leukemia, treatment with radiophosphorus induced remissions similar to those induced by roentgen therapy, but it had no particular advantage over the latter form of treatment and required a longer period of time to bring about the desired result. However, once a remission had been induced by means of roentgen irradiation, radiophosphorus was found to be effective in holding leukocyte counts near normal for long periods of time. Used in this way,

radiophosphorus eventually may prove to be a useful adjunct to treatment with roentgen rays

Radiophosphorus was ineffectual in inhibiting the progression of acute leukemia, Hodgkin's disease and multiple myeloma. However, in myeloma, treatment with the isotope afforded varying degrees of relief from pain in the bones in more than 50 per cent of our series of cases. In one case of myeloma the observation that treatment with radiophosphorus, combined with roentgen therapy, resulted not only in destruction of tumor tissue locally but in formation of new bone at the site of the original tumors, has proved of sufficient interest to warrant further study. Consequently, an investigation of the effects of combined therapy now is being carried out.

Treatment with radiophosphorus is not a difficult procedure, provided the therapist knows the rate of loss of radioactivity and the rate of excretion of the isotope. Dosage then can be adequately controlled. The chief advantages of this form of therapy are the ease of administration, the absence of radiation sickness and toxic symptoms and the concentrated effect of the irradiation on the cells of the hematopoietic organs. The principal disadvantages of the method are two: (1) since radiophosphorus enters into all phases of the metabolism of phosphorus in the body, tissues other than those one wishes to treat are irradiated and (2) once an overdose of the isotope is administered, no effective method is available for inhibiting or stopping the irradiation effect. Leukopenia, thrombocytopenia and anemia can be produced, and in order to prevent severe damage to the bone marrow, adequate observation and carefully controlled dosage are essential.

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A CONSIDERATION OF THE HYPERACTIVE CAROTID SINUS REFLEX SYNDROME

HARRY L. SMITH

THE hyperactive carotid sinus reflex continues to be a most complicated and interesting subject. In the past few years, I believe, there has been some progress in our knowledge of the physiology of the carotid sinus. I am sure that we have a better understanding of the clinical features of this subject than we had a few years ago, and this better understanding has been gained by study and observation of patients who had this condition for several years. Such study and observation have been carried out among patients who have been operated on and patients who have been treated medically.

In man and in many animals the carotid sinus is a bulbous dilatation of the first portion of the internal carotid artery. The wall of the carotid sinus is somewhat thinner than the wall of other portions of the artery. In the sinus the tunica interna is practically the same as the tunica interna of the rest of the artery. The tunica media of the sinus, however, is thinner and contains more elastic tissue and less muscular tissue than does the tunica media of the rest of the artery. The tunica adventitia of the sinus is thicker than the tunica adventitia of the rest of the artery, and contains special nerve cells called "nerve receptors." These nerve receptors are situated between the layers of collagen.

Investigators are not entirely agreed as to the complete innervation of the carotid sinus, but most of the outstanding investigators agree that the carotid sinus is supplied with branches from the glossopharyngeal, vagus and cervical sympathetic nerves, and occasionally by a few branches from the hypoglossal nerve. The afferent branch from the glossopharyngeal nerve is called the "nerve of Hering."

It has been proved by physiologists that mechanical or electric stimulation of the carotid sinus produces a combined reflex or cardiac inhibition and a decrease in the systolic blood pressure, that is, such stimulation brings about the same effect that is produced by stimulation of the central end of a depressor nerve. It is believed that one of the functions of the carotid sinus reflex is concerned with control of blood pressure and heart rate, and maintenance of an adequate circulation in the brain. It is thought by some investigators that an increase in pressure within the sinus will, by means of a reflex, cause a decrease in blood pressure and a retardation of the cardiac rate, and that a decrease in pressure within the sinus will increase the blood pressure,

accelerate the cardiac rate, increase respirations and increase the secretion of epinephrine

I do not believe that all the functions of the carotid sinus are fully known. There is not a satisfactory explanation as to why the carotid sinus in some instances becomes hypersensitive, but there is no doubt that it does.

Stimulation of a sensitive carotid sinus induces striking changes in the cardiac conduction system. The more important changes are sudden slowing of the heart rate, varying degrees of heart block, and long periods of complete cardiac standstill. In about half the patients observed at the Clinic the cardiac slowing was sufficient to cause the fainting attacks, in the other cases the slowing was absent or was too slight to be of any significance.

Stimulation of a sensitive carotid sinus by mechanical pressure produces rather marked changes in respiration. In the severe attacks the breathing becomes deep and labored. There does not appear to be a constant correlation between the labored breathing and the cardiac slowing and the fainting attacks.

Carotid sinus syncope is much more common among males than females. In the series of eighty-five patients thus affected who were observed at the Clinic the ratio of males to females was 5:1. Carotid sinus syncope is most common among middle-aged and elderly persons, it is rare among young people. In this series of cases the oldest patient was seventy-eight years old and the youngest was twenty-eight years old. The average age was fifty-six years. The chief symptoms were attacks of vertigo and spells of unconsciousness, mild convulsions may be associated with the syncopal attacks. A definite aura usually is present, this consists of weakness, lightheadedness, spots before the eyes and epigastric distress. Patients often turn pale, perspire profusely and complain of sensation of numbness in the extremities. During the attacks of unconsciousness the pupils usually dilate, during one of the induced attacks there was definite exophthalmos which receded quickly at the termination of the attack. Generally, vertigo is a prominent symptom during an attack, the patient as a rule is free from dizziness between the attacks. During the attacks of vertigo patients often stagger and occasionally they fall. The attacks of unconsciousness usually last from a few seconds to fifteen or twenty minutes, the average attack lasts one minute to four minutes. The spontaneous attacks of unconsciousness practically always occur when the patient is either sitting or standing, and rarely when the patient is lying down. Attacks of fainting occasionally are precipitated by changing the position of the body, turning the head to the right or left, or looking upward. Any pressure on the neck, such as that exerted by a tight collar or by the carrying of sacks of grain on the shoulders also may bring on attacks. It is common for episodes to occur in

barber chairs when towels are placed rather tightly around the patient's neck, and when the patient changes the position of his body rather quickly. The attacks of unconsciousness may vary from a mild attack once or twice a year to many severe attacks daily. One patient I recently observed had nineteen severe attacks in twenty-four hours. In most instances, the precipitating factors in the spontaneous attacks are unexplained.

There has not been an adequate study of the blood pressure during spontaneous attacks. In the induced attacks the blood pressure usually decreases, this decrease varies from slight-to-severe depression of blood pressure. The decrease in blood pressure was greatest in cases of hypertension. In a few instances there was a slight increase in blood pressure during the induced attacks.

In the attacks of unconsciousness the patient may have a mild or a severe convulsion. Patients practically never bite their tongues or lose control of their sphincters. Generally, the induced attacks are of shorter duration than the spontaneous ones. The diagnosis is made from the history and by inducing an identical attack by the exertion of graded pressure on one of the carotid sinuses. It should not be necessary to induce an attack by making pressure on both sinuses at the same time. I do not recommend the practice of pressing on the eyeballs to induce an attack.

Preferably, the patient should be in a sitting position, with the head tipped slightly backward and to one side and away from the side that is being examined. The sinus usually is situated just below the angle of the jaw and at the level of the upper border of the thyroid cartilage. The situation of the sinus is somewhat variable, however. The carotid bulb frequently can be palpated definitely. Pressure is exerted with the thumb, so that the sinus is compressed against the spinal column. As a rule, the characteristic response will occur within ten to twenty-five seconds. This depends on the efficiency of the examiner and the sensitivity of the sinus.

The treatment of hyperactive carotid sinus reflexes may be divided roughly into three parts.

First, when the symptoms are mild and the attacks occur at infrequent intervals, no treatment is required other than reassurance.

Second, when the symptoms are moderately severe and the attacks occur more frequently and interfere with the patient's work and activity, the patient should be instructed to avoid turning the head quickly, looking upward and stooping suddenly. The patient should avoid any constriction about the neck. Medication is indicated. Many drugs have been used for this malady. Those most commonly recommended are phenobarbital, ephedrine, epinephrine, benzedrine, atropine and diphenylhydantoin sodium (dilantin). In my experience, drugs have not been particularly satisfactory. But, of the drugs used,

phenobarbital has given the best results. The amount administered depends on the severity of the symptoms. At the Clinic we usually give $1\frac{1}{2}$ grains (0.1 gm), three times a day for one week to two weeks and then $1\frac{1}{2}$ grains twice a day for another week and then $\frac{3}{4}$ grain (0.05 gm) for several weeks. We like to administer the smallest amount that will control the episode.

Third, when the attacks are severe and occur frequently, and after a thorough course of medical management has been carried out without success, surgical treatment may be tried in selected cases. In our experience at the Clinic, this has not been too satisfactory. The surgical procedure consists of complete denervation of the carotid sinus. Some neurosurgeons recommend intracranial section of the glossopharyngeal nerve rather than operation through the neck.

In the treatment of patients who have hyperactive carotid sinus reflex there are several factors to bear in mind, first, that it is not a killing disease, and second, that the symptoms vary greatly from time to time. In some patients the condition seems to go into remission, so that the patients may be comfortable for several weeks or months without any symptoms, even when they are not receiving treatment.

THE HYPERVENTILATION SYNDROME

HADDON M. CARRYER

AN important medical problem, yet one which is often unrecognized, is the syndrome resulting from hyperventilation. Until recent years the mechanism of this disorder has been poorly understood. In 1933 and 1934 Maytum and Willis^{11, 12} first called attention to sighing dyspnea, a common form of hyperventilation, in the production of symptoms frequently confused with those of pulmonary or heart disease. Other investigators have done much to clarify knowledge of the physiologic changes observed in the course of respiratory alkalosis caused by hyperventilation. Kerr and his associates at the University of California have been particularly interested in this problem. They found an early and interesting reference to this condition which bears quotation:

"Melancholoke folke are commonly guen to sigh, because the munde being possessed with great varietie and store of foolish apparitions, doth not remember or suffer the partie to be at leisure to breathe according to the necessitie of nature, whereupon she is constrained at once to sup vp as much ayre, as otherwise would sruce for two or three time, and this great draught of breath is called by name sighing, which as it were a reduplicating of the ordinary manner of breathing. In this order it falleth out with louers, and all those which are very busily occupied in some deep contemplation. Sillic fooles likewise which fall into wonder at the sight of any beautifull and goodly picture, are constrained to giue a great sigh, their will (which is the efficient cause of breathing) being altogether distracted, and wholly possessed with the sight of the image."⁴

ETIOLOGY

The symptoms of the hyperventilation syndrome come about as the result of an increased loss from the body of carbon dioxide. This occurs from the lungs in the course of an excessive pulmonary ventilation. The usual concentration of carbon dioxide in the alveolar air is approximately 40 mm partial pressure of mercury.¹ With unduly stimulated breathing this level of alveolar carbon dioxide may be reduced to approximately a half of that value. Thus a chain reaction is initiated which in turn affects the equilibrium existing between the carbon dioxide of the alveoli and of the blood, and subsequently that equilibrium existing between the carbon dioxide and the bicarbonate of the blood. An increased alkalinity is made temporarily present in

THE DIAGNOSIS AND MANAGEMENT OF NEOPLASTIC DISEASES IN CHILDHOOD

HAROLD W DARGEON, M D *

SINCE neoplastic diseases in many instances appear to be local pathologic manifestations, it is proper to begin this review by mentioning the known principles which apply to the diagnosis and management of diseases in general. A diagnosis is the interpretation of alterations produced in an individual by the presence of disease. Management implies the care not only of the pathologic entity as such, but also of the individual who suffers from the disorder.

In neoplastic diseases of children the relationship between the growing tumor and the growing child is usually the basis on which clinical manifestations of the disease are recognized. The influence of the growing tumor on the growing individual and, on the other hand, of the growing individual upon the tumor will result in various symptoms and signs. Examples of the effect of the growing tumor on the growing individual are found in patients suffering with neoplastic diseases which because of the peculiar tissue contents of the tumors produce slight to marked alterations in skeletal and somatic growth. Such changes are found in some teratomas as well as tumors of the pineal, pituitary, thyroid and adrenal glands, and ovarian and testicular tumors. An illustration of the effect of the development of the individual upon the tumor is found in melanoma. During early childhood this tumor is almost invariably benign, but with the onset of puberty it may become malignant.

Consideration of the growing child in relation to the tumor is also highly essential when treating either surgically or by irradiation a neoplasm in the vicinity of an epiphyseal cartilage.

Management further implies adequate if not complete eradication of the tumor at the earliest time, compatible of course with the immediate and future well-being of the patient. As a corollary of this it is obvious that in children the earliest treatment must follow the earliest possible diagnosis and this in turn requires vigilant observation of the presumably normal child.

From the clinical standpoint it is preferable to *consider all tumors to be potentially if not actually incompatible with life, rather than to diagnose them as benign or malignant*. The reason for this becomes apparent when it is realized that many histologically benign tumors

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the blood as the so-called respiratory alkalosis is brought about. Numerous chemical changes occur in the body consequent to this respiratory alkalosis. Grant and Goldman recognized in 1920 that tetany could be induced by means of hyperventilation. This effect is mediated through the influence of respiratory alkalosis on the blood calcium. While no significant change in the total calcium of the blood takes place, the readily available, or ionized, portion is affected markedly. This ionized calcium is, in part, temporarily bound by the increased alkalinity present in the blood in respiratory alkalosis. The decrease in available calcium increases the excitability of the neuromuscular mechanism, thus inducing tetany.

It recently has been stressed that respiratory alkalosis will significantly alter the release of oxygen from hemoglobin within the tissues of the body.³ With a lowered carbon dioxide pressure in the blood, hemoglobin clings more tenaciously to its bound oxygen. Less oxygen is relinquished in the tissues as the blood passes through. Another factor which interferes with tissue oxygenation is the decreased blood flow as a result of contracted blood vessels in tissues low in carbon dioxide pressure.¹⁰

Clinically the hyperventilation syndrome may occur in many forms and all forms have in common one feature—increased pulmonary ventilation. This respiratory abnormality may be observed in entirely stable subjects, particularly when they are exposed to emotional stress. Most commonly, however, this syndrome is observed in tense, excessively anxious, depressed or psychoneurotic patients. Such subjects often fall into the practice of hyperventilation when placed in a situation where embarrassment would be experienced should fainting occur, such as in crowds, in a front pew in church, or preoperatively in a hospital. At such times the respiration may be increased in depth, accelerated, or both, with the insidious onset of symptoms referable to respiratory alkalosis. Such patients will realize that something is amiss and will attempt to fight off their unpleasant symptoms through further hyperventilation by forced breathing.

Alkalosis may be induced by unrecognized stimulation of respiration as described. The frequent sighing observed in tense subjects may contribute to the production of an acapnia or lowered concentration of carbon dioxide in the blood. Experimentally forced breathing will reproduce the symptoms of respiratory alkalosis. It may well be that strenuous exercise by those unaccustomed to it will lead to acapnia, particularly is this true of swimming, an activity imposing a voluntary influence on an involuntary center for respiratory regulation. Physical activities at altitudes at which oxygen pressure is decreased may lead to a washing out of the carbon dioxide of the body more rapidly than this gas can accumulate through metabolic processes.

SYMPTOMS

Following World War I White and Hahn studied large groups of subjects with and without the so-called effort syndrome. They observed sighing dyspnea in 80 per cent of such subjects. In a healthy control group this breathing irregularity was observed in but 19 per cent. They concluded that hyperventilation was responsible for the symptoms of this condition. In 1938 Soley and Shock likewise observed that hyperventilation was responsible for the symptoms of the effort syndrome. They substantiated their conclusions by carefully controlled physiologic studies of the changes occurring in the blood and alveolar air.

Gliebe and Auerback have emphasized the frequency with which hyperventilation may simulate organic disease. They have observed hyperventilation as a part of the fear reaction in emotionally unstable persons. Confronted by a situation in which he is inadequate, a patient may transfer his anxiety to any organ by a sequence of physiologic changes consequent to hyperventilation. Thus the precipitating psychic conflict may be ignored entirely as he pursues an explanation for his somatic symptoms.

The importance of hyperventilation as the so-called trigger mechanism in precipitation of manifestations of hysteria has also been emphasized. It is probable that hyperventilation contributes to the so-called acute anxiety attack.²

Because subjects who are otherwise quite stable will become subject to hyperventilation in times of anxiety or fear, this disturbance of respiration becomes of utmost importance in aviation. Faulty judgment and in-co-ordination in the course of overbreathing is one source of failure of pilots.^{7, 8, 13}

The symptoms of respiratory alkalosis are insidious and minimal in their onset, however, if measures are not taken to rectify this abnormality of breathing, they may assume an alarming character. If the patient understands his condition poorly these symptoms may induce a state of panic as he realizes that something over which he has no control is happening. An early symptom is that of lightheadedness and unsteadiness. This is entirely subjective in its beginning. As the alkalosis progresses, a sense of a vacuum which is insatiable by the deep breathing it prompts is produced in the thorax. Patients may fan themselves and glance around for the nearest exit. Often they will go out of doors or open a window in an attempt to secure more adequate respiration. Explanations such as "The air won't go down far enough," "The air is doing no good" or "I can't get a satisfactory breath" may be offered. In the thorax a sense of dull pressure is often noted. This often leads to anxiety concerning the heart. For the examining physician in such distress makes obvious the necessity for great care to exclude the pain arising from coronary artery disease.

With further hyperventilation a sense of numbness and tingling in the extremities and around the lips develops. Ultimately these pre-tetanic paresthesias are followed by spontaneous muscular twitching and then tetany of a carpopedal type. Throughout this sequence of physical changes mental astuteness is lost gradually and the loss is first apparent only in its effect on judgment and skill, but ultimately it progresses in some cases to stupor.

DIAGNOSIS

On the basis of recognition of the manifestations of hyperventilation, the diagnosis can be made readily. Should the patient be examined by a physician at a time when evidences of respiratory alkalosis are not present, the characteristic history will be the guide to a correct appraisal of the patient's complaint. Under such circumstances, the symptom of which the patient complains frequently may be reproduced by a period of forced breathing sufficient to induce respiratory alkalosis. Three minutes of moderately accelerated breathing with care to exhale the supplemental air usually will suffice. Often only a part of the patient's symptoms may be reproduced, the deficit being attributable to the lack of a fear response associated with the release of epinephrine within the body.

TREATMENT

Treatment of the hyperventilation syndrome depends largely on its diagnosis which enables the physician to offer an explanation of the condition to the patient. By avoiding the practice of forced breathing, by temporarily holding the breath, or by rebreathing air exhaled into a paper sack, the patient may bring about alleviation of his symptoms within a few seconds. Nasal, instead of oral, breathing likewise is of value in overcoming respiratory alkalosis. By means of these measures carbon dioxide is allowed to reaccumulate in the alveolar air. The most anxious patient appreciates the physician's demonstration that the terrifying sensations are not imaginary. He develops confidence that his condition is understood and becomes willing to discuss any underlying psychic factor. In many cases it is only necessary to demonstrate that the symptoms are the result of hyperventilation and to explain the nature of these symptoms to the patient. In other cases, the anxiety is more deeply motivated and prolonged psychiatric investigation and treatment may be indicated.

The recognition of the hyperventilation syndrome represents a means of explaining symptoms long known to be functional in origin but little understood. This knowledge has provided a way of adequately treating a previously unsatisfied group of deserving patients who "know something is wrong."

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THE ROENTGENOLOGIC DIAGNOSIS OF BRONCHIECTASIS BEFORE BRONCHOGRAPHY

C ALLEN GOOD

THE fact that a roentgenologic diagnosis of bronchiectasis is possible before the instillation of opaque oil into the bronchial tree is not realized as widely as it should be. For many years roentgenologists have made, and clinicians have accepted, a roentgenologic diagnosis of pulmonary tuberculosis although the basis for such a diagnosis is on very little firmer foundation than that for the prebronchographic diagnosis of bronchiectasis. The diagnosis of tuberculosis must be proved ultimately by demonstrating the tubercle bacillus; the diagnosis of bronchiectasis must be proved ultimately by demonstrating the dilated bronchus. A working diagnosis of tuberculosis is frequently made from roentgenologic findings alone while a working diagnosis of bronchiectasis more often depends on the history than on the roentgenogram.

The roentgenologic manifestations of bronchiectasis are often definite. They have been described particularly well by Andurs, Evans and Galinsky, and Joress and Robins. In the main they consist of four signs: (1) increased pulmonary markings, (2) chronic pneumonitis, (3) ring shadows or "honeycombing" and (4) loss of volume of a portion of the lungs. When more than one of these signs are present in any particular case the probability of a correct diagnosis is greatly enhanced.

MATERIAL

To determine how often the roentgenologic diagnosis of bronchiectasis could be made or suspected before resorting to bronchography, all cases of bronchiectasis which were encountered at the Mayo Clinic during the year 1945 were reviewed. Only those cases were accepted for study in which the diagnosis was proved after the instillation of opaque oil into the bronchial tree or in which the lung was subjected to gross and microscopic examination after surgical removal or at necropsy. There were 123 such cases.

ROENTGENOLOGIC MANIFESTATIONS

Increased Pulmonary Markings—The roentgenologic manifestation found most commonly in this series of cases was an increase in the prominence of the pulmonary markings. In ninety-four (76 per cent) of the 123 cases this feature was observed either alone or in combination with one or more of the other signs (table 1). It was

present alone in thirty-nine cases, and in combination with one or more of the other roentgenologic signs of bronchiectasis in fifty-five cases. It was the sign which was present in 83 per cent of the cases in which only one manifestation was seen

Normally there are seen in the roentgenogram of the thorax linear shadows which extend outward from the hilum. The distribution of these shadows corresponds to the anatomic distribution of the bronchial tree and accompanying vessels. The shadows are somewhat more pronounced in the bases and especially in the cardiophrenic angles. The width and density of these shadows decrease as the peripheral portions of the lungs are approached.

TABLE 1

ROENTGENOLOGIC SIGNS OF BRONCHIECTASIS IN 123 PROVED CASES

	Increased Pulmonary Markings	Chronic Pneumonitis	Ring Shadows or Honeycombing	Loss of Volume of Portion of Lung
Sign present alone, cases	39	2	4	2
Sign present in combination with one other sign, cases	38	21	18	13
Sign present in combination with two other signs, cases	17	12	10	4
Sign present, per cent of all cases	76	28	26	15

When bronchiectasis is present the width, density and number of these linear shadows may be increased in the involved segment of the lung. Since bronchiectasis is commonly a disease of the lower lobes, the lower lobes are the regions in which the increased markings are commonly present.

There is a wide variation in the degree in which this sign is apparent. In certain instances the shadows may be as much as 1 cm wide (figs. 138 and 139). Instead of tapering, the ends may be blunt, irregular or clubbed. In other cases the resemblance between what is normal and what is abnormal may be close. In the borderline case distinction is often difficult. In such a case the roentgenologist will find useful a large experience with the normal.

When the increase in pulmonary markings is present only in an upper lobe, the roentgenologic diagnosis is likely to be erroneous

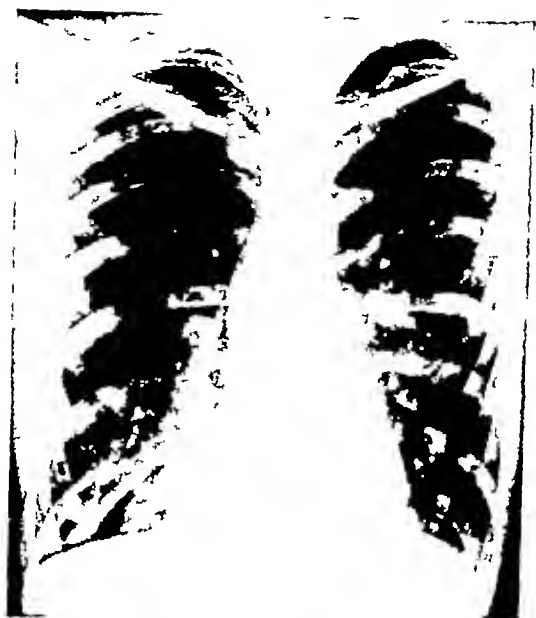


Fig 138—Marked increase in pulmonary markings in the right base together with some chronic pneumonitis. Contraction of the left lower lobe is hidden by the shadow of the heart. A bronchogram showed bronchiectasis in both lower lobes and in the lingula of the left upper lobe.



Fig 139—*a*, Marked increase in pulmonary markings in both bases together with chronic pneumonitis on the right, *b*, bronchogram which shows bronchiectasis in both lower lobes.

Since tuberculosis is the lesion which most commonly involves the upper lobes, and since the roentgenologic manifestations may resemble

those seen in bronchiectasis, such a diagnosis is sometimes mistakenly made. An example of such a case is shown in figure 140.

Andrus found an increase in the pulmonary markings in almost 100 per cent of his cases. He attributed the shadows to the changes in the bronchial walls and peribronchial tissues which are present in bronchiectasis. He preferred the term "mural bronchitis" to describe these changes.

Joress and Robins found increased pulmonary markings in 74 per cent of sixty-two cases, reports of which were collected from civilian and military sources. In twenty-nine of the thirty-seven cases of frank bronchiectasis listed by Evans and Galinsky the pulmonary markings were prominent.



Fig 140—*a*, Pulmonary markings in right upper lobe are moderately increased. The roentgenologic diagnosis was tuberculosis, *b*, bronchogram which demonstrates bronchiectasis of the right upper lobe.

It should be pointed out that patients suffering from cardiovascular disease also may exhibit increased pulmonary markings on the roentgenogram of the thorax. For this reason the presence of these shadows is not pathognomonic of bronchiectasis. Such a diagnosis is more probable if other manifestations of bronchiectasis, such as chronic pneumonitis or atelectasis, are found (fig 141).

Although an increase in pulmonary markings is the most common roentgenologic finding in bronchiectasis it is also least dependable. Because of the fact that a distinction between the normal and the abnormal is difficult in borderline cases, and because increased markings may be present in other conditions, a diagnosis of bronchiectasis will be made from the prebronchographic roentgenogram more often than can be justified by the frequency of occurrence of the disease. Confirmatory evidence must be sought in the history and eventually in bronchography, particularly in those cases in which surgical operation is contemplated or doubt is cast on the diagnosis.



Fig 141.—Increased pulmonary markings in both lungs with associated "honeycombing," particularly in the left base, and chronic pneumonitis. Bronchiectasis in both lower lobes and in the right middle lobe was demonstrated by means of bronchography.

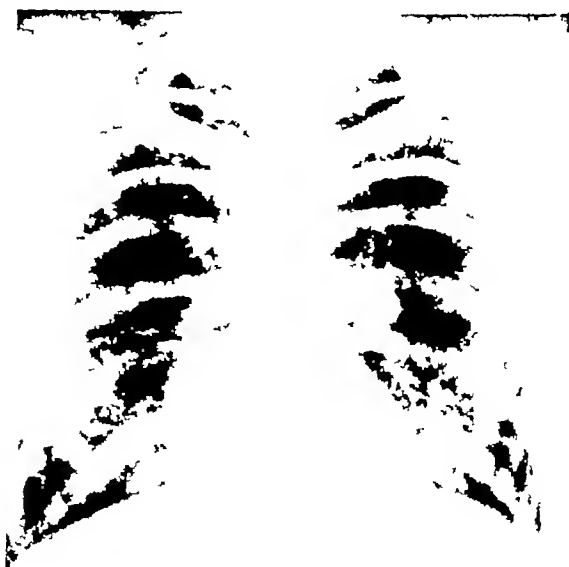


Fig 142.—Chronic pneumonitis in the left base. There is associated increase in pulmonary markings on both sides and some "honeycombing" in the right cardiophrenic angle. A bronchogram demonstrated extensive bronchiectasis involving all lobes of both lungs.

Pneumonitis—Evidence of chronic pneumonitis is present in almost every case of bronchiectasis in which tissue is examined microscopically after surgical removal of the involved lung. This pneumonitis is manifested roentgenologically in far fewer instances than is manifested on microscopic examination of tissue. In this series of 123 cases, 28 per cent showed roentgenologic evidence of frank pneumonitis (table 1). Its appearance was that of poorly circumscribed shadows or collections of shadows, frequently irregular, often dense but sometimes translucent. These shadows are the same as those seen in other types of bronchopneumonia. For the most part, pneumonitis is found accompanying one of the other signs of bronchiectasis (fig 142). It was present alone in only two instances in this series (fig 143).



Fig 143—*a*, Pneumonitis in the left base. One year previously roentgenograms in the same case had showed pneumonitis in both bases. This is an example of chronic recurring pneumonitis, *b*, bronchogram which shows bronchiectasis in both lower lobes made six months previous to *a*.

Evans and Galinsky emphasized that one of the most reliable diagnostic signs of bronchiectasis is the presence of pneumonitis which takes longer than two weeks to disappear. The ordinary "primary atypical pneumonia" resolves completely in from ten to fourteen days. When pneumonitis persists longer, bronchiectasis should be suspected. These authors found twenty-eight instances of slowly resolving pneumonitis in thirty-seven cases of frank bronchiectasis.

Pneumonitis was present in 80 per cent of cases in Andrus' series and in 9 per cent of cases listed by Joress and Robins.

Ring Shadows or "Honeycombing"—Some degree of "honeycombing" was found in 26 per cent of the cases in this series. Usually this was present in combination with one or more of the other signs, and most frequently in combination with increased pulmonary markings.

have resulted in the death of the patient. From the child's standpoint it is actually of little concern whether a tumor is histologically benign or malignant if the end result, in either case, is death.

A satisfactory classification of children's tumors should be based on a histogenetic or histologic basis. For clinical purposes, however, the following classification has been found useful.

I. Cysts secondary to fetal structural defects

- A. Those resulting from failure of involution of normal fetal tracts, e g , thyroglossal and branchial cysts, Rathke's pouch cyst.
- B. Aberrant tissues, e g , accessory thyroid gland
- C. Cystic disease, e g , polycystic kidney, pulmonary, hepatic or pancreatic cyst.

II "True" tumors of embryonal or differentiated structure

- A. Teratomas, teratoid tumors and dermoids
- B. Tumors of the following sites
 - 1. Nervous system
 - 2. Eye and orbit.
 - 3. Bones
 - 4. Lymphatic and blood-forming organs
 - (a) Leukemia
 - (b) Lymphosarcoma
 - (c) Hodgkins disease.
 - 5. Genitourinary tract.
 - 6. Somatic structures, including
 - (a) Skin
 - (b) Fat
 - (c) Connective tissue
 - (d) Muscle
 - (e) Vessels
 - (f) Nerve
 - (g) Synovia

Other tumors such as those of the breast, gastrointestinal tract and endocrine glands also occur but they are rare during childhood and will not be included in this discussion.

Cysts Secondary to Fetal Structural Defects

Branchial Cyst—This cyst usually presents no problem in diagnosis. There is a swelling of the lateral portion of the neck, sometimes extending to the midline. It may not appear until some time after birth and not uncommonly does not become manifest until adult life. This cyst may also occur intrathoracically, producing symptoms referable to the respiratory system. The diagnosis, although generally made only at operation, may be suspected by demonstrating an intrathoracic mass in roentgenograms.

Thyroglossal Duct Cyst—One of the most common congenital cysts is that arising from the thyroglossal duct. It appears usually in

(table 1) On the roentgenogram the appearance may be that of a diffuse honeycombing of the involved segment of lung (fig 144), or there may be discrete rings which contain air or air and fluid (fig 145).

Andrus expressed the belief that these ring shadows are due, not to bronchiectatic cavities, but to emphysematous air sacs. He found this sign present in 85 per cent of the cases in his series. Joress and Robins noted honeycombing in 19 per cent of their sixty-two cases.

Decrease in Volume of a Portion of the Lung.—A significant decrease in volume of the affected lobe or portion of the lung was found in 15 per cent of the cases in this series (table 1). This decrease in volume is thought by some authors to be due to atelectasis and by

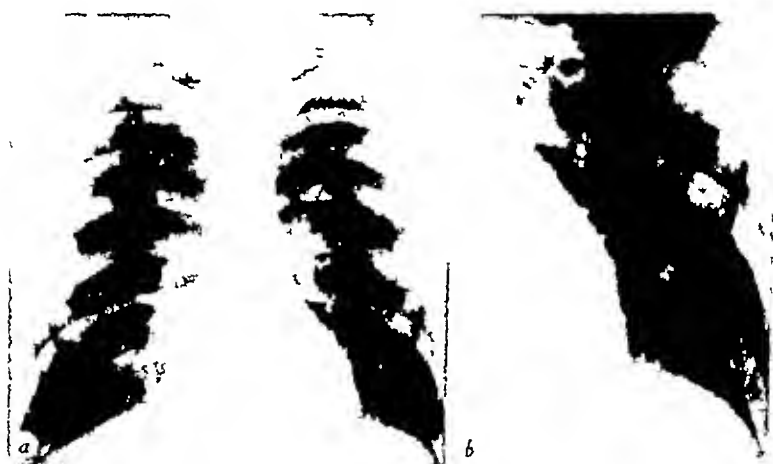


Fig 144—*a*, Same case as in figure 142. Roentgenogram made nine months after that shown in figure 142 and shows "honeycombing" in both bases. *b*, Localized view of the base of the left lung where the "honeycombing" is especially well shown.

others to be due to shrinkage secondary to chronic pneumonitis. Since the lower lobes are most commonly involved, the roentgenologic appearance is frequently that of a triangular shadow of increased density in the cardiophrenic angle. The apex of the shadow is directed toward the hilus (figs 145 and 146). If the right middle lobe or the lingular portion of the left upper lobe is involved, the shadow of increased density lies just below the hilus rather than in the cardiophrenic angle, although roughly triangular in shape, the apex of the shadow is directed toward the lateral wall of the thorax rather than toward the hilus. If an upper lobe is involved the triangular shadow is situated above the hilus and borders the shadow of the mediastinum.

Andrus found some degree of displacement of the heart, diaphragm or interlobar fissure in 90 per cent of the cases in his series. He stated that this displacement was a sign that atelectasis was present to some



Fig 145—*a*, Ring shadows, some of which show fluid levels, on the left. Contraction of the left lower lobe with triangular shadow of increased density partially covered by the shadow of the heart. *b*, Localized view of left base which shows ring shadows and contracted lobe

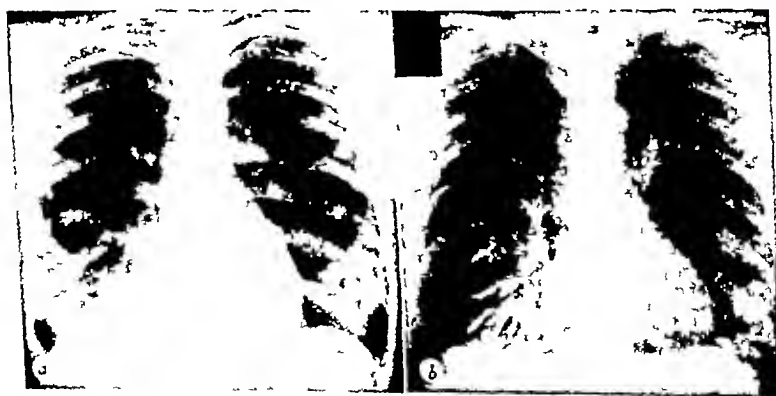


Fig 146—*a*, Contraction of a portion of the right lower lobe associated with increased pulmonary markings, *b*, bronchogram which shows bronchiectasis of the middle and lower lobes on the right.

degree. Joress and Robins noted atelectasis in 17 per cent of their cases, while Evans and Galinsky observed evidence of contracted lung in eleven of thirty-seven cases of frank bronchiectasis.

No Signs Present.—In eleven cases in this series the roentgenograms of the thorax were considered to be normal (fig 147) This represents an incidence of about 9 per cent In five other cases nothing abnormal was recognized at the time the roentgenogram was first seen, but a review disclosed one of the four signs to be present, usually obscured by the overlying shadow of the heart



Fig 147—*a*, No evidence of bronchiectasis can be noted, *b*, bronchogram in the same case which shows bronchiectasis in the left lower lobe and in the lingula of the left upper lobe

Because bronchiectasis may exist without obvious roentgenographic signs, bronchography should be performed whenever the history and physical findings suggest the presence of the disease

RELIABILITY OF ROENTGENOLOGIC DIAGNOSIS

Although signs indicative of bronchiectasis were present in about 90 per cent of the 123 cases in this series, actually the diagnosis was made fifty-six times and suggested twenty-five times In the forty two other instances a descriptive or erroneous report was given twenty-six times and a negative report sixteen times

In several instances a diagnosis of tuberculosis was made because of involvement of one of the upper lobes (fig 140) It is probable that this error will continue to be made The increases in pulmonary markings caused by tuberculosis and by bronchiectasis are similar. Unless fibrosis or calcification is present there may be nothing in the roentgenologic appearance to distinguish the two conditions Since tuberculosis is present in the upper lobe more frequently than is bronchiectasis, it will be chosen as the diagnosis in the few cases of bronchiectasis of the upper lobe which are encountered

The converse is also true A diagnosis of bronchiectasis will probably be made from a study of the roentgenograms in most cases of

tuberculosis involving the bases of the lungs if there is no involvement of the upper lobes

Thirty-seven of the patients in this series were operated on because of bronchiectasis. Lobectomy or pneumonectomy was the operation performed. Surgical operation is useful in the treatment of bronchiectasis if the disease is unilateral. In order to be certain that the contralateral side is not involved, as well as to prove the presence of the lesion, all patients on whom operation is contemplated should have bronchographic studies after the instillation of opaque oil into the bronchial tree.

SUMMARY AND CONCLUSIONS

A presumptive or working diagnosis of bronchiectasis can be made from roentgenographic evidence in a majority of cases before resorting to bronchography. The signs on which such a diagnosis depends are (1) increased pulmonary markings, (2) chronic pneumonitis, (3) ring shadows or "honeycombing" and (4) decrease in volume of a portion of the lung. If more than one of these signs are found in an individual case the probability of the presence of bronchiectasis is greatly enhanced. A combination of three of these signs is almost pathognomonic of the disease.

The final unequivocal diagnosis of bronchiectasis depends on bronchography. In 9 per cent of the 123 cases in this series no evidence of disease was seen in the prebronchographic roentgenogram. Bronchography is necessary also to define the limits of involvement, particularly in those cases in which surgical operation is contemplated.

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CLINICAL RECOGNITION AND MANAGEMENT OF THE UREMIC STATE

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In 1827, Richard Bright first described the disease which bears his name and nine years later, in a more detailed account, wrote as follows

Again the patient is restored to tolerable health, again he enters on his active duties or he is perhaps, less fortunate,—the swelling increases, the urine becomes scanty, the powers of life seem to yield, the lungs become œdematous, and, in a state of asphyxia or coma, he sinks into the grave, or a sudden effusion of serum into the glottis closes the passages of the air, and brings on a more sudden dissolution Should he, however, have resumed the avocations of life, he is usually subject to constant recurrence of his symptoms, or again, almost dismissing the recollection of his ailment, he is suddenly seized with an acute attack of pericarditis, or with a still more acute attack of peritonitis, which, without any renewed warning, deprives him, in eight and forty hours, of his life Should he escape this danger likewise, other perils await him, his headaches have been observed to become more frequent, his stomach more deranged, his vision indistinct, his hearing depraved he is suddenly seized with a convulsive fit, and becomes blind He struggles through the attack, but again and again it returns, and before a day or week has elapsed, worn out by convulsions, or overwhelmed by coma, the painful history of his disease is closed.

More than a hundred years have elapsed since the foregoing observations were made and yet this classic description of the uremic state leaves little to be desired in the way of addition or change The multiple symptoms and signs associated with the uremic state are well known, as are the deviations from normal which may occur in the body fluids, but many questions relating to the pathogenesis and mechanism of production of uremia remain unanswered

DEFINITION

Uremia may be defined as the symptom complex which results from renal insufficiency with retention of urinary constituents in the body fluids The word "uremia" was coined in 1840, by Piorry and l'Héritier, to designate a toxic state brought about by failure of the kidneys to accomplish adequate detoxication of the blood Since then, almost every symptom occurring in the course of cardiovascular-renal disease has been considered, at one time or another, as being uremic in origin Early in the present century, two distinct types of clinical uremia were recognized (1) the asthenic or azotemic type, in which the symptoms were thought to be due to urea poisoning and (2) the convulsive or chloruremic type, in which convulsive seizures were ascribed to retention of chlorides in the blood.

It remained, however, for Volhard in 1918, to clarify the concept by his division of the syndrome into true uremia and pseudo-uremia. He described three different symptom complexes, only one of which was dependent on renal insufficiency, although the other two often occurred in association with it. He characterized as "acute pseudo-uremia" the symptoms of violent headache, convulsions and signs of increased intracranial pressure, which, in his opinion, were due to cerebral edema. The fact that these symptoms were often observed in cases of acute nephritis, eclampsia and other conditions not associated with retention of urea or other nitrogenous substances in the blood led Volhard to believe that the symptoms were not the result of renal insufficiency, even though they occurred usually in cases of renal disease. He designated as "chronic pseudo-uremia" such symptoms as syncopal attacks, paresthesias, transient hemiparesis and hemiplegia, aphasia, transient visual disturbances and mental changes. It was his contention that such symptoms were vascular in origin, occurring in cases of severe benign or malignant hypertension, and that, although they were frequently encountered in association with renal impairment, accumulation of nitrogenous waste products in the blood was not a part of the clinical picture. Oppenheimer and Fishberg also have distinguished between renal insufficiency and such vascular symptoms, which they have included under the term "hypertensive encephalopathy" and which in their opinion are vasospastic in origin rather than due primarily to cerebral edema. In the present review, discussion will be concerned only with true uremia.

OCCURRENCE

The uremic state may occur as a complication of any of a number of conditions which impair the formation of urine in a normal manner or its flow along the urinary tract. It may develop rapidly as a complication of acute renal insufficiency or the onset may be gradual, with its presence unsuspected until, in an advanced stage, the symptoms and signs develop with alarming suddenness.

The underlying causes of uremia may be classified into three major groups:

- 1 **Prerenal or Extrarenal Uremia.**—In this form faulty elimination by the kidneys is secondary to factors acting principally on the tissues, the composition of the blood or the circulation of blood through the kidneys. Conditions in which such a situation may occur are many and space will permit enumeration only of the most important: (1) severe and protracted vomiting, such as is encountered in patients with pyloric or intestinal obstruction, (2) excessive loss of intestinal contents in severe diarrheas or intestinal fistulas, (3) acute or chronic hepatic disturbances—so-called "hepatorenal syndrome", (4) diabetes with acidosis, either a comatose or a precoma-

tose state, (5) the crises of Addison's disease, (6) traumatic or surgical shock, (7) peripheral circulatory collapse associated with conditions such as severe infections or burns, (8) profuse hemorrhage, especially from the gastro-intestinal tract, (9) congestive heart failure.

In all of these conditions death may ensue with severe impairment of renal function and yet, at necropsy, the anatomic structure of the kidneys may be found intact. Among the factors which have been thought to be important in the impairment of renal function in the foregoing conditions are dehydration, hypochloremia, alkalosis, acidosis and abnormalities of circulation (low arterial pressure) resulting in decreased renal blood flow. There is ample experimental and clinical evidence that each or all of these factors may play a vital role in functional impairment of the kidneys, the predominant factor depending largely on the underlying condition. That adequate renal blood flow is necessary for adequate renal function has long been known and the mechanism by which decreased blood flow may cause functional impairment is well understood. However, the exact mechanism by which changes in the composition of the blood may produce renal insufficiency still remains obscure.

2 Renal Uremia.—In this form impairment of renal function is secondary to organic disease in the kidneys themselves. Any of the diseases affecting the kidneys ultimately will end in uremia when so much of the renal parenchyma is destroyed that the remaining portion is unable to carry on adequate function. If progression of renal damage is gradual, the patient often is able to make a relatively asymptomatic adaptation to greatly impaired renal function, uremic symptoms developing only in the terminal phase of the disease. On the other hand, severe acute renal insufficiency is not well tolerated by the patient and early onset of the uremic state, which may be fatal, must be expected. The incidence of uremia in different forms of renal disease varies greatly and is, in part, dependent on the portion of the functioning renal unit involved by the disease process. Some of the more important diseases in which uremia occurs, may be enumerated as follows: (1) in chronic glomerulonephritis uremia is frequent and is the most common cause of death, (2) uremia may occur in acute glomerulonephritis but its incidence is much lower than in the chronic phase of the disease, (3) although renal impairment may be encountered in severe benign hypertension, severe renal insufficiency and uremia usually occur only in the malignant or premalignant type, (4) renal amyloidosis, (5) polycystic disease of the kidneys, (6) acute necrotizing nephroses, such as are caused by mercury, bismuth, carbon tetrachloride or other toxic agents, if fatal, generally terminate in acute uremia, (7) although it is seldom encountered in acute pyelonephritis, severe renal insufficiency with attendant uremia frequently occurs in the later stages of bilateral chronic pyelonephritis.

(8) while embolic phenomena in the kidneys in the course of sub-acute bacterial endocarditis almost never produce sufficiently widespread damage to lead to uremia, diffuse secondary glomerulitis occurs fairly often in severe enough degree to make renal insufficiency and uremia a conspicuous part of the clinical picture

3 **Postrenal Uremia.**—In this form renal insufficiency and the subsequent development of the uremic state are brought about by interference with the flow of urine beyond the kidneys. Any lesion which produces complete mechanical obstruction to urinary flow ultimately will be responsible for the development of uremia, unless the obstruction can be removed before marked irreparable damage to renal parenchyma has occurred. Among such conditions may be listed the following: (1) prostatic hypertrophy with obstruction, either benign or malignant, (2) ureteral or urethral strictures, (3) renal or ureteral calculi, (4) vesical neoplasms with obstruction of the ureteral orifices, (5) pelvic carcinoma (especially of the cervix) with ureteral obstruction. The clinical picture of uremia as it occurs in any of the foregoing conditions is almost identical with that occurring in diseases affecting the kidneys themselves, a fact which supports the belief that the uremic state actually results from insufficient renal excretion.

PATHOGENESIS

It is beyond the scope of this paper to discuss the vast amount of literature and numerous hypotheses which have been evolved in an attempt to explain the mechanism underlying this unfortunate train of events. Most of the older investigators looked for a single toxic substance as the basis for uremic symptoms and, as stated previously, at one time or another almost every urinary constituent has been incriminated.

Probably the oldest unitary hypothesis for causation of the uremic state is that of retention of urea. This belief has been fostered and supported by the fact that of all urinary constituents retained in the blood in renal insufficiency, urea accumulates in the greatest proportions. Against the hypothesis of accumulation of urea as the single causative factor is the relatively low toxicity of the substance. It has been shown experimentally that large quantities of urea must be ingested before symptoms similar to those encountered in uremia are produced. Leiter injected urea intravenously into dogs and found that, in order to produce fatal symptoms, the quantity of urea injected must approximate 1 per cent of the animal's weight, blood urea levels averaging 1,383 mg per 100 c.c. of blood. Hewlett and his co-workers found that by ingesting large quantities of urea and producing elevation of blood urea levels as high as 240 mg per 100 c.c. of blood, headache, somnolence, vertigo and nausea could be produced. However, clinical uremia has been observed in patients whose blood urea

levels were as low as 100 mg per 100 c c, whereas other patients have displayed much higher concentrations of urea in the blood for long periods, yet with no symptoms suggestive of uremia. Still other patients with severe renal insufficiency may have astoundingly high levels of urea in the blood, in some instances, terminal elevations to 500 to 600 mg per 100 c c. of blood have been recorded. It seems likely that uremia cannot be ascribed entirely to urea intoxication, however, it is possible that when abnormally large amounts of urea accumulate in the blood and tissues, they may contribute to the uremic picture

Retention of creatinine, magnesium or potassium likewise has been thought to be the sole cause for the production of uremia. However, there have been numerous experiments and much clinical information has been accumulated to show that, while any or all of these substances may be retained in the blood in renal insufficiency, the degree of retention is not constant and cannot explain the multiplicity of symptoms which occur

Intoxication by retained organic acids, increased osmotic pressure of the blood, dehydration, increased destruction of body protein, accumulated products of intestinal putrefaction, guanidine retention and toxic urinary constituents or "nephrollysins" of an unknown nature, all have received attention as the possible causative factor of the uremic state

None of the numerous hypotheses which have attempted to explain the wide variety of symptoms of uremia on the basis of retention of a single toxic substance are supported by adequate proof. It is necessary, therefore, to adhere to the present-day concept which holds that the uremic state probably is dependent on retention in the blood and tissues of not one but multiple intoxicants. Uremia is "a complex auto-intoxication, the variegated clinical picture being the summation of the effects of retention of various urinary constituents"⁴

Uremia may produce its clinical picture through the failure of renal function alone. However, in many cases, and particularly in those instances associated with advanced renal disease, the symptoms of uremia may be intensified or accentuated by loss of chloride and dehydration, due partly to vomiting or diarrhea, and partly to impairment of renal tubular function

CLINICAL PICTURE

The onset of the uremic state is usually, although not necessarily, gradual and insidious. Between the time when retention of waste products begins to occur and the onset of uremic symptoms, there is usually a latent period of several weeks, months or even years. A good example of this latent period is seen in cases of mechanical anuria or acute urinary suppression, wherein the patient may feel

relatively well for several days before the early symptoms of uremia develop. In many instances, however, the uremic state may be ushered in suddenly, the prodromal symptoms having passed unobserved.

In general, the symptom complex of uremia is essentially the same, whether the underlying pathologic change is prerenal, renal or post-renal in origin. The clinical picture may vary from patient to patient or may change from day to day in the same patient, with symptoms referable to one system or another occupying the predominant role. The general symptoms to be observed are evidences of varying degrees of cachexia, dehydration of the skin and mucous membranes and a progressively developing urinous odor to the breath. Emaciation is common in uremia, although in early stages it may be masked by the presence of peripheral edema. Dehydration, which is a common manifestation, usually is due to loss of large amounts of fluid either by polyuria, vomiting or by diarrhea and an insufficient fluid intake due to nausea and vomiting. The urinous odor, a frequent symptom in uremia, is thought to be due to bacterial decomposition of the high urea content of the saliva, which has been shown to vary with the urea content of the blood. Not all patients who have uremia exhibit this characteristic odor and this symptom may be entirely absent even in the presence of abnormally high values for urea in the blood.

Central Nervous System.—Probably the earliest nervous symptoms of uremia are easy fatigability and muscular weakness, associated with listlessness and mental apathy. The patient may move more slowly and may complain of drowsiness. Yet despite a progressive tendency to mental and physical retardation, he may have difficulty in sleeping and may awaken at the slightest noise. He may doze off several times during a conversation, yet arouse easily and become instantly alert. At times, overalertness, excitement and increased irritability may be conspicuous. As the picture becomes more definite, progressive dulling of the sensorium may occur, punctuated by periods of excitement and disorientation. The patient may appear semistuporous during the day and suffer from insomnia, agitation or delirium during the night.

Headache is one of the most common symptoms of uremia but usually is generalized in location and dull rather than severe. Intense paroxysmal headaches occurring in the course of uremia should be strongly suspected of being due to cerebral edema or hypertensive cerebrovascular changes rather than of being a true uremic symptom. Vertigo may occur in the course of uremia but is more frequently noted if there is associated hypertensive encephalopathy.

Muscle twitchings are commonly observed in uremia. They are seen usually as fibrillary twitchings occurring in the muscles of the trunk, extremities or face. As the uremic state progresses into the terminal stages, generalized convulsions may occur, in varying degrees of fre-

the midline of the neck, invariably at or above the level of the hyoid bone. Clinically, it may resemble a hemangioma. If excision of any mass in this region is contemplated the possibility of a thyroglossal cyst should be considered.

"True" Tumors of Embryonal or Differentiated Structures

Teratoma and Teratoid Tumor.—These growths may appear in many regions of the body: brain, thorax, abdomen, pelvis and sacro-coccygeal region. Those which present externally may be diagnosed



Fig 58—Meningocele, teratoid tumor (M K, female aged 1 month). The two tumors were observed at birth. The dark mass is gastric mucosa, which showed active peristalsis and constant secretion of mucus. Roentgenographically there was no connection with the gastrointestinal tract. A spina bifida was noted roentgenographically and demonstrated at operation.

by palpation. Such tumors may contain intestines, and visible and palpable peristalsis may be demonstrated. If the growth occurs intracranially, intrathoracically or intra-abdominally, pressure symptoms may be produced. The proximity of the tumor to certain vital structures may produce functional disturbances of various kinds throughout the body. Inasmuch as they frequently contain tissue of high physiological potency, such as adrenal gland, they may be associated with extraordinary metabolic disturbances. A case of teratoma

quency, severity and duration. Subjectively, the patient may complain bitterly of frequent, painful cramps in voluntary muscle groups. Deep tendon reflexes are usually increased and may remain brisk until the late symptom of coma develops, whereupon they may be decreased. The active reflexes, muscular twitchings, muscle cramping and convulsions are thought by some to be related to a decrease of ionized calcium in the blood. However, cases have been reported in which the foregoing symptoms have occurred with little or no abnormality of serum calcium levels. At present, the exact mechanism for production of these symptoms of increased neuromuscular irritability remains speculative. In some cases, true hypocalcemic tetany may be observed, with characteristic carpopedal spasm and positive Chvostek's and Trousseau's signs. It has been shown experimentally that in the presence of acidosis, more free calcium is liberated, an observation which may explain why tetany is not encountered more frequently in uremia.

Finally, depressive symptoms progress to the point where terminal coma develops and death ensues after a period lasting from several hours to several days. Whether retention of toxic phenol derivatives plays a significant role in the production of depressive symptoms and coma or whether disturbed chloride metabolism may be an important factor are questions yet to be answered.

Harrison and Mason in their excellent monograph on the pathogenesis of uremia made a statement regarding the central nervous system in uremic animals which might well be applied to uremic patients:

In observing these uremic animals one gains the impression that the nervous system is being subjected to two different and opposite influences, the one tending to stimulate it and the other to depress it. In some animals the irritative phenomena have the ascendancy. In others the depressive manifestations are more outspoken. More frequently the same animal successively displays the one and then the other group of symptoms and not uncommonly, although paradoxically, the same dog may at a given time exhibit signs both of stimulation and depression of the nervous system.

Skin.—There usually is marked pallor of the skin and mucous membranes in cases of long-standing chronic or severe uremia. This is most noticeable in uremia associated with advanced renal lesions and is fundamentally due to the marked degree of anemia which is an almost inevitable accompaniment of severe renal disease. With development of the uremic state, an already existing anemia may be aggravated by significant loss of blood, a uremic symptom which will be discussed later. Pruritus, which may become intense, is a very common symptom and may occur at any stage in the development of the syndrome. It may become sufficiently severe to interfere seriously

with the comfort and rest of the patient and may resist all attempts at palliation. Because of this, it is common to note extensive scratch marks and factitial lesions on the extremities, on the trunk and even on the face. The pathogenesis of this annoying symptom is not clear.

Cutaneous eruptions of variegated appearance may be noted. There have been described papular, vesicular, licheniform, eczematoid and erythematous lesions, in addition to frequently noted purpuric and ecchymotic areas. The exact nature and cause of the cutaneous eruptions in uremia are unknown but they are suspected of being related in some way to retention in the skin and tissues of unidentified toxic substances. It has been suggested that the sensitivity of the skin may be altered, for it is known that patients who have uremia may be unusually susceptible to drug eruptions.

A rare but spectacular phenomenon occurring late in the course of uremia is "uremic frost," often noticeable on the face, neck and thorax and giving the appearance of a fine coating of frost on the skin. This symptom, due to deposition of crystalline urea on the skin, usually portends death in the near future.

Blood.—As mentioned previously, anemia is invariably present in uremia and may be very severe. Profound anemia is seen more frequently in uremia of renal origin than in prerenal or postrenal uremia, unless renal insufficiency is relatively long standing or severe. The nature of the anemia is not entirely clear but it is thought to be due to depression of bone marrow function and not to increased blood destruction. This supposition is supported by the fact that serum bilirubin values are rarely increased in cases of renal insufficiency. Both hemoglobin and erythrocytes are affected, the values for these sometimes reaching appallingly low levels.

There usually is little or no abnormality in the leukocytes unless the picture is complicated by the presence of some intercurrent infection.

A hemorrhagic tendency is prominent and occurs frequently in cases of uremia. Epistaxis, bleeding from the gums, hemoptysis, hematemesis, melena and hematuria are common occurrences and may reach serious proportions. Vaginal bleeding may occur in female patients, sometimes to a degree where the patient is suspected of having an intra-uterine malignant lesion. Cutaneous hemorrhage also may occur and it is fairly common to find purpuric areas in the conjunctivas, mucous membranes and diffusely over the skin surfaces, as well as larger areas of subcutaneous extravasation of blood. Satisfactory explanation for this hemorrhagic diathesis has yet to be found, despite the fact that in some cases the blood coagulation time is increased.

Cardiovascular System—Almost all types of chronic renal disease which ultimately lead to uremia are associated with hypertensive cardiovascular involvement. In such cases in which uremia develops,

angiospastic retinitis, hypertension, cardiac hypertrophy, congestive heart failure and pericarditis may be expected. Acute pulmonary edema frequently occurs as a late event and may be responsible for fatal termination of the disease. An occasional patient who has chronic renal disease dies in uremia without associated hypertensive or cardiac involvement, suggesting that while hypertensive cardiovascular disease and uremia are frequently coexistent, the mechanisms of their production are distinct and different.

The clinical picture of congestive heart failure is well known and need not be discussed in detail. Left ventricular failure with cyanosis, dyspnea, orthopnea and pulmonary congestion, or venous engorgement, tender enlargement of the liver, dependent edema and ascites associated with right ventricular failure may be conspicuous in the uremic picture. Auricular fibrillation may be noted or extrasystoles frequently may occur. Pulsus alternans is noted fairly frequently and gallop rhythm often is observed.

The incidence of pericarditis in uremia is relatively high. While its nature and pathogenesis have been the subject of discussion for many years, the exact cause for, and mechanism of, its production still remain problematical. In many cases in the course of uremia a pericardial friction rub may develop. In some cases, the patient may complain of precordial pain or discomfort, or the rub may be entirely asymptomatic. It may be evanescent and disappear after a few hours or it may persist for days. It has been known to occur, subside and recur at a later date in the same patient. The development of a pericardial friction rub usually signifies an unfavorable prognosis and relatively early death, although patients have been known to live for weeks or months after an episode of uremic pericarditis.

Respiratory System.—Dyspnea, orthopnea, episodes of nocturnal dyspnea and acute pulmonary edema are common complications of uremia but are due to cardiac failure and subsequent pulmonary congestion and are not related directly to renal insufficiency.

Slow, deep respirations similar to the typical Kussmaul breathing of diabetic coma are commonly observed in the late stages of uremia, particularly after coma develops, and are probably due to acidosis.

Periodic breathing and typical Cheyne-Stokes respiration may occur but are more likely to be related to associated cerebrovascular disease than to disturbances of renal function.

Hiccup, a frequent symptom in uremia, is presumed to be central in origin. Always annoying and exhausting to the patient, hiccup in the later stages of the uremic state may be almost impossible to control.

Gastro-intestinal System.—Patients who have uremia often complain of dryness and burning in the mouth. These symptoms may, in part, be on the basis of dehydration but are more likely associated with the development of "uremic stomatitis," which may progress to

an ulcerative or even a gangrenous process. Bleeding from the gums is a fairly common occurrence. The mucosal lining of the mouth may be covered with patches of membranous white exudate and the tongue may become swollen to the point that feeding is rendered difficult. Parotitis has been reported as occurring in uremia, as has painful esophagitis with dysphagia, the latter condition probably occurring on the same basis as stomatitis.

Anorexia, nausea and vomiting are encountered commonly and may be the earliest symptoms of uremia. Loss of appetite may be present for months before the onset of other cardinal symptoms. Vomiting may occur at any time, before or after meals, and in the later stages may become almost continuous and uncontrollable. If there is associated cerebral edema, vomiting may be projectile. The vomitus may or may not be blood tinged and frequently has an ammoniacal odor. Little is known of the causation of these symptoms in uremia, although it is presumed that in some way they are initiated by the effect of the accumulation of toxic substances in the blood. Since the nonprotein nitrogen content of the gastric juice in uremic patients is usually as high or higher than that in the blood, some have felt that vomiting may be a symptom initially compensatory in nature, serving as an extrarenal means for the excretion of urea and other waste products. However, if this be true, a vicious cycle is established, for, although excessive vomiting may produce alkalosis or at least limit the degree of acidosis, there can be no doubt that severe chloride deprivation over a period of time can only serve to aggravate the existing renal insufficiency.

Many patients who have uremia are severely constipated, however, as the disease progresses, diarrhea may ensue. They may pass frequent large watery stools of high nitrogen content, which may or may not be blood tinged. Diarrhea usually develops as a symptom of uremic enteritis or colitis, with the formation of ulcerated areas along the course of the intestinal tract. Occasionally massive melena may occur. Some investigators have suggested that uremic enteritis may be due to irritation of the lining of the bowel by the high ammonia concentration of the contents. It would appear that uremic enteritis and colitis are parts of an increased reaction of the entire gastro-intestinal tract to uremic inflammation and ulceration, the exact mechanism of which is unknown.

It should be re-emphasized at this point that the clinical picture in uremia may be variable, the symptoms occurring in different combinations or varying in intensity from patient to patient or from time to time in the same patient. The picture is influenced greatly by the underlying cause. Uremia on the basis of long-standing chronic renal disease is usually more severe and the symptoms more striking than that due to prerenal or postrenal causes, unless, in the latter group

the disease process has been present sufficiently long to produce significant permanent damage to the renal parenchyma secondarily

ALTERATIONS IN THE COMPOSITION OF THE BLOOD

Changes in the chemical composition of the blood in renal insufficiency and uremia may be produced in four general ways, the relative importance of which may vary with the circumstances involved (1) potential urinary constituents may be retained, (2) the retained urinary constituents may produce secondary chemical changes in the blood, (3) water and certain electrolytes may be reabsorbed inadequately by the failing kidney owing to insufficient tubular function, (4) the kidney may be unable to synthesize ammonia, resulting in loss of fixed base from the body

Potential urinary constituents which are retained in the blood in renal insufficiency may be divided into three groups 1 The first group consists of the nitrogenous end products of protein catabolism, as well as phosphate and sulfate resulting from breakdown of amino acids and of other substances containing phosphorus and sulfur Consequently, urea, nonprotein nitrogen, creatinine, uric acid, phosphate and sulfate values in the blood will be found elevated in varying degrees, depending on the severity of renal impairment 2 Retention of chlorides in the blood may occur in severely oliguric or anuric patients who have not yet lost excessive chloride by vomiting Since chlorides are excreted predominantly by the kidneys, in certain obstructive lesions of the lower part of the urinary tract or after the ingestion of large quantities of salt in the presence of renal insufficiency, retention of chloride and high values for plasma chloride may result 3 Indican, phenols and other products of intestinal putrefaction which normally are absorbed from the bowel and excreted in the urine are usually retained in the blood in cases of uremia and may be directly or indirectly responsible for many of the symptoms observed

That retention of certain urinary constituents may cause secondary changes in the composition of the blood is illustrated by the fact that retention of phosphate in the blood tends to cause a reciprocal depression of the serum calcium levels Also, accumulation of organic acids in the blood tends to depress plasma bicarbonate levels and produces acidosis with decrease in the level of the carbon dioxide combining power of the blood

Impairment of tubular function results in failure of absorption of various electrolytes, particularly chlorides, with consequent chloride deficiency Uremic patients, as stated previously, lose a great deal of chloride by vomiting and it has been shown that damaged kidneys may continue to excrete chloride even after the plasma chloride value has fallen below the level which ordinarily would produce achloric urine in a healthy person Sodium values in the blood, as a rule, are

not markedly affected in cases of uremia but tend to remain at or about normal levels. Occasionally, the value for serum sodium may be found to be increased and, in some cases, the level is observed to be markedly decreased. Some patients whose kidneys are seriously damaged show a remarkable ability to excrete potassium with normal or near normal values for potassium in the serum, whereas others show rather marked potassium retention even to the point of manifesting electrocardiographic evidence of potassium intoxication. Serum magnesium levels are affected slightly or not at all by the uremic state and it is doubtful whether magnesium retention is sufficient to account for any of the symptoms or signs of uremia, unless it is complicated by magnesium therapy (magnesium sulfate or magnesium citrate as purgatives), in which event the serum magnesium values may rise to high levels and may be responsible for some of the toxic symptoms, notably increased drowsiness or coma.

The diagnosis of uremia without the aid of the laboratory may be extremely difficult, for the onset of symptoms may be insidious and the symptom complex closely resembles any one of a number of other situations such as hypertensive encephalopathy, cerebral accident or diabetic acidosis and coma. The most important laboratory adjunct is a study of the chemical composition of the blood. The changes in the various organic and inorganic constituents of the blood which may be observed have been described already. For all practical purposes, three fundamental determinations will give the desired information. 1. If the blood urea or nonprotein nitrogen is normal or only slightly elevated, it can be said with certainty that the patient's symptoms are not caused by uremia. I have never observed uremia in a patient with a blood urea of less than 100 mg per 100 c.c. of blood. The opposite is not always true, elevation of blood urea or nonprotein nitrogen to high levels does not necessarily indicate that the symptoms observed are on a uremic basis, although, if the characteristic symptom complex is present in association with markedly increased blood urea or nonprotein nitrogen levels, uremia should be suspected until excluded. 2. Estimation of plasma chlorides will indicate the presence of significant hypochloremia and furnish definite indication for replacement therapy. 3. Determination of the carbon dioxide combining power will indicate whether the patient is in alkalosis or acidosis and, as in the case of the plasma chlorides, will influence the decision of the physician as to the choice of fluid to be administered parenterally.

PROGNOSIS

Prognosis in cases of uremia is governed to a great extent by the nature and severity of the underlying pathologic process which has produced the marked renal impairment of which the uremic state is

symptomatic In general, prerenal uremia carries a much more favorable outlook for the patient than renal uremia, provided the underlying disease can be corrected and uremia controlled before the process has advanced to a terminal phase The prognosis in cases of uremia associated with chronic renal disease is, for the most part, exceedingly grave and fatal termination may be expected within a matter of days or weeks, although some patients with slowly progressive chronic uremia have been known to live several months or years In certain cases of acute tubular nephrosis due to such causes as poisoning with mercury, bismuth or carbon tetrachloride, sulfonamide intoxication or transfusion with incompatible blood, in which renal insufficiency and uremia occur as a result of anuria due to acute tubular damage, the outlook may be favorable if uremic symptoms can be controlled until healing occurs to a degree where formation of urine once more is resumed The outlook in cases of postrenal uremia depends on the nature and extent of the tubular lesion, whether or not it is amenable to correction, duration of the tubular dysfunction and the extent of secondary glomerular involvement

MANAGEMENT

Since it is seen that the uremic state may develop under so many different circumstances, may occur in varying degrees and may present such variegated clinical manifestations, a discussion of the principles involved in its management must, for the most part, be general, for the condition of the patient from day to day may necessitate changing the plan of treatment, not once, but several times The fundamental aims can, however, be broadly discussed under four headings (1) reduction of the excretory load on the kidneys, (2) attempts to improve renal function, (3) attempts to promote extrarenal excretion of waste products, and (4) symptomatic treatment

Reduction of the Excretory Load on the Kidneys.—The principal factor in accomplishment of this aim is consideration and regulation of the diet Since retention of waste products of protein breakdown is important in the production of uremia, one of the fundamental considerations is that of restriction of intake of protein Protein in the diet should be limited to some extent but should not be restricted to a point at which breakdown of body protein occurs Furthermore, it must be remembered that the patient may have hypoproteinemia with edema as part of the underlying pathologic process and too stringent reduction of protein intake may serve only to decrease plasma proteins further and aggravate the edematous state, as well as to impair the patient's nutritional state Much investigative work has been done and much has been written regarding the minimal amount of exogenous protein required daily to maintain a patient in nitrogen equilibrium It is agreed generally at the present time that approximately

1 gm. of protein per kilogram of body weight per day is sufficient to meet the basic needs of the average person. On this basis, a diet containing 40 to 80 gm. of protein daily should be adequate and yet not excessive. There is no reason to believe that there is any difference between any of the protein foods (white meat, red meat, eggs, milk) in so far as their effect on renal function is concerned.

There need be no restriction of the volume of fluid ingested if edema is not a complicating feature. It should be borne in mind that dehydration is an extremely common occurrence in uremia and relatively large quantities of fluid are necessary not only to combat this complication but also to aid the failing kidneys in eliminating as much accumulated waste as possible by means of a large urinary volume. In the great majority of severely uremic patients, adequate oral intake of fluid is inhibited by persistent and intractable vomiting and it is necessary to resort to parenteral administration of fluids, the type and amount of which will be discussed later. Anuria, edema or cardiac failure may present difficult problems in deciding the optimal fluid intake for the patient. In so far as edema is concerned, consideration of the existing renal insufficiency should take precedence, for its implications are by far more serious than those of edema. Overhydration in the presence of cardiac failure may increase the load on the failing left ventricle with aggravation of pulmonary congestion or production of acute pulmonary edema. On the average, a daily fluid intake of 2,000 to 3,000 c.c. either by mouth or parenterally would seem to be sufficient. In the presence of cardiac failure, it may be wise to keep the volume at the lower figure or reduce it even further. In the presence of extreme dehydration or excessive loss of fluid, volumes up to 4,000 c.c. or more may be required.

It is wise to restrict, in moderate degree, the sodium chloride in the diet, even though there may be no tendency to edema, for in the presence of severe renal insufficiency, the ability of the kidneys to excrete salt is diminished. However, in patients who have lost chloride by vomiting or who have hypochloremia, it may be wise to increase the amount of salt in the diet, or use 0.9 per cent solution of sodium chloride parenterally. If significant edema is present, more stringent salt restriction should be enforced, because of the water-binding tendency of sodium and its tendency to increase edema.

Since the patient's appetite usually is poor, the diet should be made light but as attractive as possible. Carbohydrates may be used freely and foods of high caloric value should be employed in order to keep the bulk as low as possible. The patient may have difficulty in assimilating large quantities of fat and, therefore, the volume of fat in the diet should be kept reasonably low.

Attempts to Improve Renal Function.—It has been mentioned previously that an increased fluid intake may, in some instances, aid

failing kidneys in trying to eliminate accumulated waste products through production of a relatively large urinary volume, as a compensatory mechanism for the inability of kidneys to concentrate urine adequately. Intravenous administration of fluids also may have some effect in increasing circulating blood volume and thereby augmenting renal blood flow. This function and that of replacing tissue fluid and extracellular fluid lost through dehydration are the principal means by which fluids are of value in the management of renal insufficiency. It should be emphasized again that caution must be exercised in the volume of parenteral fluid used in the presence of edema and more particularly in the presence of cardiac failure.

The type of fluid used for intravenous therapy is, in most cases, extremely important and should receive serious consideration. Glucose, in either 5 or 10 per cent concentration, makes a very desirable solution for intravenous use. In cases of edema the glucose solution should be made up in distilled water, whereas, if vomiting has been persistent and the plasma chlorides are found to be low, it is advisable to use glucose made up in 0.9 per cent solution of sodium chloride. In general, it is wise to give not more than 2 liters of fluids by the intravenous route daily, and these at different intervals, if the total daily fluid intake can be supplemented satisfactorily by the oral route. In the presence of uremic acidosis, 250 to 500 c.c. of 5 per cent solution of sodium bicarbonate may be given intravenously, usually with improvement in the state of acidosis and frequently with noticeable improvement in the clinical condition of the patient. Sodium lactate solution in volumes of 500 to 1,000 c.c. may be used for this purpose instead of sodium bicarbonate if desired. Administration of alkali should be considered if the carbon dioxide combining power falls significantly below a level of 40 volumes per 100 c.c. of plasma, and attempts should be made to maintain it at a level as near 50 volumes per 100 c.c. as possible. A 10 c.c. ampule containing $3\frac{3}{4}$ grains (0.24 gm.) of theophylline ethylenediamine (aminophylline) added to each liter of fluid given intravenously has been found in many cases to enhance the value of intravenous therapy and promote more effective diuresis. Should dyspnea, tightness in the chest, cough or distressing palpitation occur during the course of intravenous administration, it is advisable to decrease the rate of flow or discontinue administration entirely, lest pulmonary congestion or acute pulmonary edema ensue.

When renal insufficiency is present in sufficiently severe degree to produce uremia, most diuretics fail to exert their expected effect of increasing urinary volume. Xanthine diuretics may be tried with relative impunity but the results from their administration have been discouraging. There is no place in the treatment of uremia for mercurial diuretics and their use is to be strongly condemned, for in the presence of severe renal insufficiency, mercury may be retained and

produce further renal damage. Acid salt diuretics likewise are not indicated in cases of renal insufficiency if the level for urea in the blood exceeds 100 mg per 100 c c. In uremic patients, use of potassium salts may lead to retention of potassium in the blood and significant potassium intoxication, use of ammonium salts supplies an additional amount of the ammonium radical to be used in the synthesis of more urea, and use of the chloride salts may tend to aggravate further an already existing acidosis.

Digitalis is indicated only if the symptoms of myocardial failure develop in the course of uremia. However, a word of caution should be injected at this point. In the presence of renal insufficiency, with inability of the kidneys to excrete the drug satisfactorily, smaller doses may be indicated in order to accomplish the desired therapeutic effect and prevent complicating symptoms of digitalis intoxication.

If distressing and refractory edema on the basis of hypoproteinemia is present in association with renal insufficiency and severe nitrogen retention, cautious intravenous administration of a solution of acacia may be tried. This substance serves to raise the osmotic pressure of the blood depressed by loss of plasma proteins and its use may be attended with some degree of diuresis and lessening of the amount of peripheral edema. The patient usually is able to tolerate 500 c c of 6 per cent solution of acacia on alternate days for three administrations but if, during the course of injection, any untoward symptoms should develop, administration should be discontinued immediately.

Promotion of Excretion by Extrarenal Routes—The bowels should be kept open and moving freely, for by this route moderate amounts of nitrogenous waste products may be excreted. Diarrhea, which may occur in the course of uremia, should not become a matter of concern unless it reaches serious proportions. Some amount of excess nitrogen is also excreted in the vomitus of uremic patients. The use of purgatives is to be deprecated, owing to their effect in weakening the patient. Magnesium sulfate especially should be avoided, since retention of the magnesium ion may be directly or indirectly responsible for some of the toxic symptoms encountered.

The amount of nitrogen removed from the body through sweating is relatively small and is not great enough to play a significant role in reducing the high levels in the blood. Consequently, attempts to promote extrarenal excretion by induced diaphoresis are inadvisable because of its marked dehydrating and weakening effect on the patient. The amount of waste products removed by venesection is likewise relatively small and consequently the procedure should be reserved for use only for the relief of associated congestive heart failure.

In many cases acute renal failure and uremia in patients who have reversible renal lesions need not be fatal if toxic waste products can be eliminated by means of some extrarenal route during the period

of hepatic origin which produced hypertension has been recorded in the Children's Tumor Registry by Dr Benjamin Kramer of the Jewish Hospital of Brooklyn

Dermoid Cyst.—Like the teratomas, a dermoid cyst may occur in many parts of the body but may not produce equally profound physiological changes. As a rule, the growth is discovered by the discovery of a mass. If it is situated in a body cavity, symptoms of pressure may be the only manifestations.

TREATMENT OF TERATOMAS AND DERMOID CYSTS—The treatment of choice for tumors of this group is surgical removal as early as is feasible, particularly for the teratomas and allied varieties of neoplasms, which frequently become malignant.

Cystic Disease.—A pulmonary cyst may usually be diagnosed by x-ray studies without difficulty. In many cases the cyst persists for a number of years without producing symptoms. Those of the abdominal viscera or of the kidney may be diagnosed by the presence of a mass which must be differentiated from other intraperitoneal enlargements, also from inflammatory tumefactions.

TREATMENT—The treatment of the cystic diseases mentioned above is preferably expectant, although surgery may be indicated in certain instances as, for example, in infected polycystic kidney.

TUMORS OF NERVOUS SYSTEM

Tumors of the nervous system include intracranial neoplasms and growths involving cord, peripheral nerves and sympathetic nervous system.

INTRACRANIAL TUMORS

The intracranial tumors of childhood comprise a wide variety of neoplasms which arise not only from brain tissue but also from blood vessels, meninges and other structures within the cranial cavity. While apparently not among the more common varieties of childhood tumors, intracranial neoplasms nevertheless form an important group for several reasons.

First, from a diagnostic standpoint, the symptoms are many and varied depending upon the type and site of the tumor, so that it is necessary to differentiate many systemic disorders from them.

Furthermore, from a therapeutic standpoint, it is evident that the mere presence of a tumor per se is not the sole determining factor in the outcome of a case. Involvement of important cerebral structures by the close proximity of the tumor may preclude a successful surgical result.

Finally, from a prognostic standpoint the outcome does not wholly depend on the histologic structure of the existing neoplasm—the particular area involved, the extent of the growth and the injurious effects

of marked renal impairment. Some of the lesions which may be amenable to this method of treatment are (1) injury or obstruction of the tubules due to intravascular hemolysis, such as the "crush injury" syndrome, or "globinuric nephrosis" following transfusion with incompatible blood, (2) injury of the tubules following sulfonamide intoxication, or poisoning with mercuric chloride, carbon tetrachloride, and so forth, (3) acute renal suppression following prolonged shock or reflex anuria after bilateral retrograde pyelography or manipulation of a ureteral calculus. Several methods have been attempted in the past, including reciprocal transfusions and plasmapheresis, both of which have been discarded for clinical use because of impracticability of the first method and the tendency of the second method to produce serious depletion of the plasma proteins. Two methods which were first described a number of years ago and have recently received revived attention are the method of external dialysis or vividiffusion first attempted by Abel, Rowntree and Turner in 1914, and lately given clinical application by Kolff and Berk and the method of internal dialysis or peritoneal lavage first described by Canter in 1923. Both methods appear to show considerable promise in suitable cases. The subject is too large to lend itself to a detailed discussion in this report but an excellent review may be found in a recent paper by Fine, Frank and Seligman.

Symptomatic Treatment.—In many cases of advanced chronic renal disease, when uremia has progressed to late stages, it may not be possible to do much more than attempt to control distressing symptoms as they arise and do whatever is possible to make the patient more comfortable. Sedatives may have to be used freely and in relatively large doses in order to control headache, restlessness, insomnia and delirium. It always, however, should be borne in mind that patients who have uremia may be more susceptible to drug intoxication than those with adequate renal function. If acetylsalicylic acid, acetophenetidin, bromides and codeine fail to control the patient's symptoms, it may be necessary to resort to morphine. Barbiturates such as pentobarbital sodium (nembutal) may be sufficient to allay the symptoms if given at close enough intervals and in large enough doses. If the patient is afflicted with persistent vomiting, $1\frac{1}{2}$ to 3 grains (0.1 to 0.2 gm) of pentobarbital sodium or 3 to 6 grains (0.2 to 0.4 gm) of sodium amytal by rectum may be indicated. Tincture of opium in doses of 10 to 20 minims (0.6 to 1.2 c.c.) every three to six hours may be helpful or it may be necessary to resort to paraldehyde in doses of 4 to 8 c.c. by mouth or 8 to 15 c.c. by rectum in order to secure rest for the patient. Chloral hydrate, one of the time-honored hypnotics, may be used in doses of from 5 to 20 grains (0.3 to 1.3 gm) in solution either orally or rectally. When muscular twitchings develop sedation should be pushed further, and if convulsive seizures develop, it

may be necessary to use 3 grains (0.2 gm) or more of sodium amytal intravenously

Vomiting may be difficult or impossible to control and may seriously hamper other attempts at treatment It may be necessary to stop all administration of fluids and medications by mouth, relying on the parenteral route for fluids, nutrition and sedation Frequently, daily gastric lavage with a solution of sodium bicarbonate will diminish vomiting and relieve the patient of nausea and gastric distress Diarrhea may become intractable, however, a trial of one of the opium derivatives, such as tincture of opium or camphorated tincture of opium, may be attended with some degree of relief

Local applications, as a rule, fail completely to allay the intense pruritus which often torments these patients and it may be necessary to rely entirely on sedation for relief Ergotamine tartrate administered subcutaneously has been suggested but its frequent use is not advised in patients who have evidence of hypertensive cardiovascular disease

If muscle twitchings or cramps occur in the presence of a lowered calcium level in the blood or if there are clinical signs of tetany, such as carpopedal spasm or positive Chvostek's or Trousseau's sign, calcium should be administered either by the oral or by the intravenous route Calcium lactate or tribasic calcium phosphate may be given in large doses (4 to 8 drams [16 to 31 gm] daily) by mouth However, since absorption of calcium from the gastro-intestinal tract is slow at best, the intravenous route is preferable From 10 to 20 cc of calcium gluconate may be given intravenously one to three times daily as indicated

The use of iron and liver has proved futile in combating the severe anemia which almost invariably accompanies marked renal insufficiency Blood transfusion appears to be the only satisfactory method of restoring the blood picture to anything approaching normal levels Sometimes, the anemia is extremely stubborn and multiple transfusions may be indicated It is a well-known fact that patients who have advanced renal insufficiency respond poorly to transfusion and the administration of 500 cc of compatible blood may be followed by a violent generalized reaction It is much less hazardous and more comfortable for the patient if the 500 cc. unit of blood is divided into three portions of 175 cc., 175 cc. and 150 cc., and given at a slow rate on three successive days

In summary, one gains the impression that, although volumes have been written in an attempt to clarify the subject of uremia since the first clinical description one hundred and eleven years ago, the basic factors in the mechanism of its production are still unknown and the final chapter has, as yet, to be written Since this symptom complex may develop as a complication of pathologic processes outside the kidneys or associated with reversible renal lesions, as well as in the

course of advanced chronic organic renal disease, early recognition of the uremic state and prompt institution of adequate and attentive treatment are of the utmost importance and can, in many cases, reward the physician with marked amelioration of symptoms or an eventual return of the patient to an improved state of health

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RHEUMATOID SPONDYLITIS: QUESTIONS AND ANSWERS

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AND
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REMEMBERING the famous epigram "A woman is a constipated biped with a pain in her back"⁶⁸ physicians expect most women to have a backache and are generally not disappointed. Chronic backache is not so common among men, especially among young men. When it occurs, one should think of rheumatoid spondylitis.

"The war brought spondylitis into prominent interest." This observation, made in 1922^{31, 69} and referring, of course, to World War I, could be applied with equal pertinency to World War II.^{8, 11, 12, 47} Because of the frequency of rheumatoid spondylitis, physicians are becoming increasingly interested in it and are attempting to establish better criteria for its early diagnosis and more adequate treatment. To this end we shall give brief answers to thirty common questions concerning rheumatoid spondylitis. For this report our answers will be given in synoptic form and are of course not complete. These opinions are based on our continuing clinical experiences, on a reasonable familiarity with current literature and on a study of 1,035 cases of this condition, made recently by one of us (H F P)^{64, 65}

CLINICAL DEFINITION

1 What Is Rheumatoid Spondylitis?—Rheumatoid spondylitis is an inflammatory disease of unknown origin which generally begins in the sacro-iliac joints and progressively involves the apophyseal joints of the spinal column, the paravertebral muscles and ligaments and the costovertebral and costochondral junctions. There occur inflammation, destruction and generally osteitis of adjacent joints with rarefying and condensing arthritis in apophyseal joints, painful spasms and contractures in paravertebral muscles and calcification of paravertebral ligaments (fig. 148). Joints of hips sometimes become affected, less often those of extremities, shoulders very occasionally. Hence rheumatoid spondylitis is chiefly a disease of the spinal column or torso.

In considering the clinical pathology of rheumatoid spondylitis one must remember that the only true diarthrodial joints of the spinal column, those which possess synovial membranes, are the small apophyseal joints (the "facets"). The bodies of the vertebrae do not form true joints, with the intervertebral disks they form synchondroses

which differ from the true spinal joints almost as much as the symphysis pubis differs from a hip joint. It is the apophyseal joints which are chiefly affected in rheumatoid spondylitis.

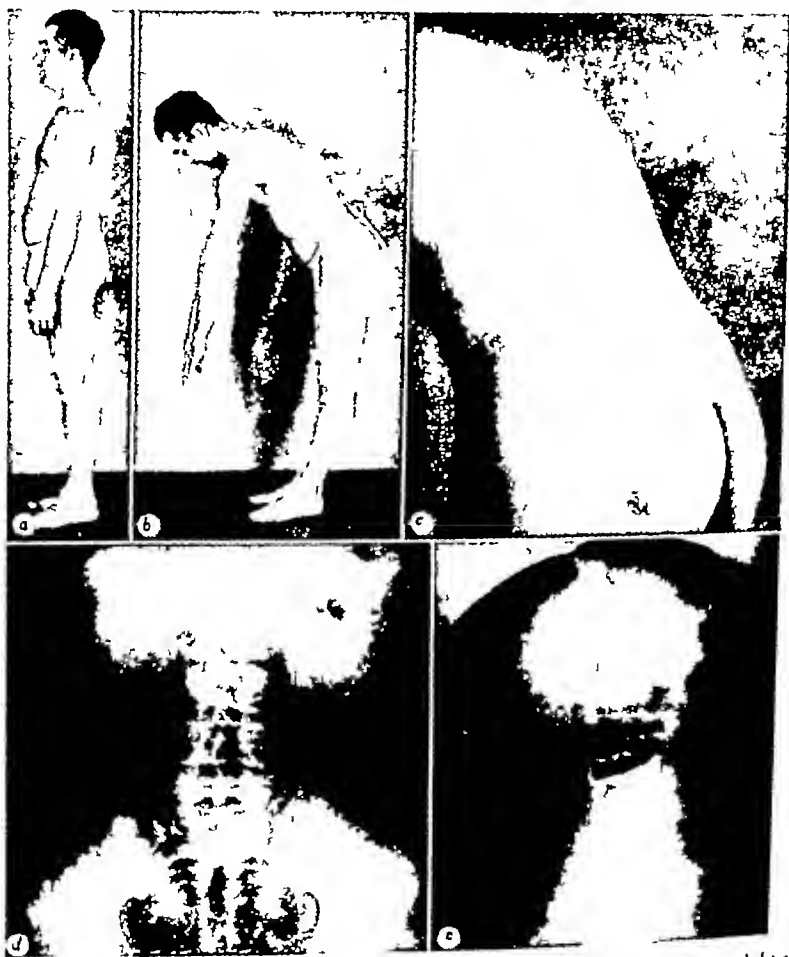


Fig 148—Man, aged thirty-seven years, who had had rheumatoid spondylitis for nine years. He could stand erect (a) but could not bend forward farther than as shown in b. If a patient has rheumatoid spondylitis without losing the lumbar lordotic curve (a), this curve remains present on forward bending (c), whereas in normal persons it is obliterated on forward bending. Persistence of the lumbar lordotic curve is less common than flattening of the lumbar lordotic curve in cases of rheumatoid spondylitis. Roentgenograms (d and e) revealed destructive arthritis and osteitis in the sacro-iliac regions and marked calcification of the ligaments in the thoracic and upper lumbar regions.

Some writers choose to distinguish between "spondylitis—disease of vertebral bodies," "spondylarthritis—disease of apophyseal joints"

and "spondylosis ossificans ligamentosa—disease of spinal ligaments"^{61 62} Other writers distinguish between spondylitis rhizomelica, ankylosing spondylitis, Marie-Strumpell's disease, Bechterew's disease and so forth. In the light of the present imperfect knowledge of these affections most rheumatologists currently prefer to regard them as clinical varieties of one general condition for which we prefer the term "rheumatoid spondylitis" as adopted by the American Rheumatism Association.

2. Is Rheumatoid Spondylitis the Spinal Equivalent of Rheumatoid Arthritis of Peripheral Joints?—Probably yes. Authorities differ rather sharply on this question.^{12, 20, 60, 63} Some regard rheumatoid spondylitis as an entity quite distinct from rheumatoid arthritis (of peripheral joints). The following differences are noteworthy: (1) Sex incidence: rheumatoid arthritis affects women about two or three times as often as men, rheumatoid spondylitis affects men about nine times as often as women. (2) Age incidence: rheumatoid arthritis tends to affect persons aged twenty-five to forty years, rheumatoid spondylitis tends to affect younger patients, aged fifteen to thirty years. (3) Calcification of juxta-articular ligaments is rare in rheumatoid arthritis of peripheral joints, calcification of paravertebral ligaments is very common in rheumatoid spondylitis. (4) The subchondral osteitis which occurs in rheumatoid arthritis of peripheral joints is largely of a rarefying nature, the subchondral osteitis of sacro-iliac joints in rheumatoid spondylitis tends to produce osseous density and sclerosis. (5) Subcutaneous fibrous nodules occur fairly frequently in cases of peripheral rheumatoid arthritis, they apparently do not occur in cases of rheumatoid spondylitis unaccompanied by involvement of peripheral joints.^{49 64} (6) Iritis affects patients who have rheumatoid spondylitis two or three times more often than it affects those who have peripheral rheumatoid arthritis.⁶⁴ (7) Agglutinins to hemolytic streptococci are present in the blood in much lower concentrations and the plasma phosphatase is increased more often in cases of rheumatoid spondylitis than in those of peripheral rheumatoid arthritis.^{19 27 54} (8) More or less complete spontaneous remissions are said to occur much oftener in rheumatoid spondylitis than in peripheral rheumatoid arthritis.⁵⁵ (9) Chrysotherapy is considered effective in a significant percentage of cases of rheumatoid arthritis but ineffective against rheumatoid spondylitis. (10) Roentgen therapy may be of value in rheumatoid spondylitis but is considered valueless in peripheral rheumatoid arthritis.^{13 77, 78}

Supporting the view that rheumatoid spondylitis is the spinal equivalent of peripheral rheumatoid arthritis are the following points: (1) In cases of rheumatoid spondylitis there sometimes develops arthritis of peripheral joints clinically indistinguishable from peripheral rheumatoid arthritis without spondylitis. (2) The pathologic reactions

in the affected hips and peripheral joints of rheumatoid spondylitis are identical with those of rheumatoid arthritis without spondylitis^{1, 61} (3) In certain cases in which peripheral joints are affected first, classic rheumatoid spondylitis later develops (4) The pathologic reactions in the (diarthrodial) apophyseal joints of patients who have rheumatoid spondylitis are said to resemble those of classic rheumatoid arthritis without spondylitis^{8, 23}

In view of the pathologic similarities and despite the notable clinical differences we would conclude tentatively that rheumatoid spondylitis is the spinal equivalent of rheumatoid arthritis of peripheral joints

CLINICAL FEATURES

3 What Is the Relative Frequency of Rheumatoid Spondylitis and Rheumatoid Arthritis?—Among civilians rheumatoid spondylitis is only a sixth to a sixteenth as frequent as rheumatoid arthritis (peripheral joints) The ratio of rheumatoid spondylitis to peripheral rheumatoid arthritis has been reported as follows 1.13 at the Arthritis Clinic, Presbyterian Hospital, New York, 1935,^{27, 82} 1.16 at the Lahey Clinic, Boston, 1940,³⁸ 1.11 at the Desert Sanatorium of Southern Arizona, Tucson, Arizona, 1941²⁸ At the Clinic in recent years the ratio has been 1.6, probably owing to a high degree of suspicion and to our special search for rheumatoid spondylitis⁶¹

Among soldiers the relative incidence of rheumatoid spondylitis to peripheral rheumatoid arthritis is much greater, 1.3 to 1.2. Thus on the medical service at Hoff General Hospital, California, one patient who had rheumatoid spondylitis was admitted for every three who had rheumatoid arthritis involving peripheral joints alone⁸ At the Army Rheumatism Center at Army and Navy General Hospital, Hot Springs, Arkansas, about a third of all cases of rheumatoid arthritis were of rheumatoid spondylitis⁴⁷

The frequency of the disease among soldiers has been explained thus (1) rheumatoid spondylitis has a predilection for men of military age, (2) the strenuous physical exertions of army life and training brought to light cases of mild and early rheumatoid spondylitis, including many previously present but undiagnosed

4 Who Is Most Likely to Develop Rheumatoid Spondylitis?—Most often affected are males aged fifteen to thirty years

In from 80^{35, 73, 70} to 90 per cent^{17, 19, 38} of all cases of rheumatoid spondylitis the patient is male Of 1,035 persons who had rheumatoid spondylitis admitted to the Clinic from 1935 to 1943, inclusive, 90 per cent were male (931 males, 104 females)

Initial symptoms may occur at any age in the Clinic series they occurred in persons from four to sixty-three years old The average age of these patients at the onset of symptoms was twenty-seven years

The onset of symptoms was prior to age thirty years in 74 per cent, prior to age forty years in 91 per cent and between fifteen and thirty-five years of age in 80 per cent.⁶⁵

The relation of occupation to the incidence of the disease has not been thoroughly studied. Scott⁶³ noted the frequency of the disease in athletic young men. However, the disease was not more common among manual workers than among sedentary workers studied by Golding, 73 per cent of his patients had led sedentary lives. This suggests that the recent high incidence of the disease among soldiers may have been due more to their age and sex than to the physical exertions of military life and that the latter merely aggravated initial symptoms sufficiently for an early and prompt diagnosis to be made.

5 **What Is the Cause of the Disease?**—Nobody knows. A French concept that rheumatoid spondylitis is related to gonorrhea,^{28 30} a concept once viewed sympathetically by certain American physicians,^{19, 53-60} remains quite unproved.^{14, 35 64 82} The ill-considered notion that rheumatoid spondylitis is related to hyperparathyroidism has been discarded. Miller regarded rheumatoid spondylitis, not as a clinical entity, but as a pathologic end result of several etiologic factors, but this was speculation. The ideas relating the disease to a sacro-iliac infection,⁷² tuberculosis, developmental anomalies of the lumbar portion of the spinal column, focal infection or familial or hereditary factors remain without significant support. The disease is not necessarily related to trauma.^{33, 64, 73} Presumably, but not certainly, the cause of rheumatoid spondylitis is the same as that of peripheral rheumatoid arthritis.

6 **What Is the Usual Course of the Disease?**—In most cases the course of the disease is fairly typical. It usually starts insidiously in one or both sacro-iliac regions, producing here and in the buttocks muscular soreness and tenderness which may be more or less constant and progressive, or often intermittent and remittent. Sometimes these early symptoms are mild, transient and relatively unnoticed, the patient, unaware of the potentially disabling and progressive nature of his disease, may not seek medical care. This stage of the disease has sometimes been called "the stage of sacro-ileitis."^{8, 33} As the disease involves the synovial membranes of the lumbar apophyseal joints, pain increases and there may develop sudden "catches" related to motion or trauma. The paravertebral muscles become chronically or intermittently spastic with the development of stiffness of the spinal column, the "spinal stage" of the disease. The patient cannot now bend forward readily or completely and as he attempts forward motion the lumbar muscles tighten, holding the lumbar portion of the spinal column stiff and preventing the normal obliteration of lumbar lordosis (fig 148). Spasms of the lumbar muscles may be quite painful and disabling. This involvement of

paravertebral muscles is in large part a functional and defensive mechanism to prevent motion in the inflamed joints but it may also be in part pathologic, resulting from localized intramuscular inflammation³²

By the time that this stage has been reached, certain constitutional manifestations have probably developed (as they do in peripheral rheumatoid arthritis) elevation of the sedimentation rate, development of mild secondary anemia, some loss of appetite and weight, excessive fatigue and occasionally mild fever Sciatica and lumbar root pains may have developed, with pain on coughing and sneezing, and as the thoracic region becomes involved intercostal and precordial pains and muscular tenderness may ensue, perhaps with further bowing of the back.

The paravertebral ligaments, especially the anterior common ligament, probably become affected fairly early in the disease but at first their participation cannot be shown roentgenographically Sooner or later a process of calcification begins to affect these ligaments as if nature sought some way to stiffen the spinal column protectively, at the same time relieving the muscles of this task with its unfortunate by-product of the painful muscle spasms If during the processes of paravertebral muscle spasms and ligamentous calcification the patient "favors" his back unduly and makes no attempt to prevent or correct the tendency to the development of spinal flexion, severe spinal deformity may develop, the spinal column becoming "frozen" in a badly bent position as the ligaments calcify (fig 149)

In a sense, the worse the disease gets locally—that is, the farther the pathologic process develops in each affected joint—and the sooner the ankylosing stage is reached, the better the patient is likely to feel and the faster the active part of the disease will be accomplished in this particular region When the sacro-iliac and apophyseal joints become destroyed and ankylosed, pain lessens, as the ligaments calcify, limiting thereby still further the motion of inflamed spinal joints and muscles, symptoms lessen and often cease entirely except for the residual limitation of motion In this residual stage, the "stage of the poker back," the previously present constitutional abnormalities tend to disappear, hemoglobin values may return to normal and gains in appetite and weight may occur

In most cases the sacro-iliac joints and the lumbar and thoracic portions of the spinal column bear the brunt of the disease, and the neck, hips and shoulder joints remain essentially unaffected although contiguous muscles and fibrous tissues may be transiently involved After a variable number of years symptoms disappear, the spinal column may be rather stiff or quite stiff with little or no permanent loss of body height, the thorax may be rather flat and immobile, hips are free and the patient's disability is only moderate, one which can be

accommodated to, one consistent with a useful self-supporting existence

Such is the ordinary course of the disease. But there are many variables, and, as Boland and Present have stated, the symptoms and findings at any one time in a given case are dependent on (1) the severity, rate of progression and duration of the disease, (2) the extent



Fig. 149—Man, aged forty-three years, who had had rheumatoid spondylitis for twenty-two years. The spinal column was ankylosed in a kyphotic position (a). Note the abdominal wrinkles resulting from the kyphosis (b).

of spinal involvement, and (3) the activity of the process at individual levels of the spinal column. The disease may start and end in sacro-iliac joints, progressing no further (fig. 150). See also fig. 154. Less often, it begins in the cervical or thoracic region rather than in the lower part of the back. It may spread up or down, or stop at any level, or it may "by-pass" a contiguous region to affect a more

produced by the intracranial hypertension also determine the prognosis

The varieties to be discussed are those which are most frequently observed in clinical practice. Other types are not considered unimportant but are omitted because of their rarity.

The sequence of symptoms will be determined not only by the location of the tumor within the cranial cavity but also by the particular area of the brain involved. The majority of intracranial tumors in childhood are subtentorial. The time at which the different clinical signs appear is helpful in many cases in the differentiation between cerebellar and supratentorial tumors. Some of the more common symptoms are those resulting from increased intracranial pressure, namely headache, vomiting, sometimes nausea, papilledema, abducens paralysis, and hydrocephalus. The roentgenogram shows separation of the suture lines, increased digital markings, and thinning of the posterior clinoids in older children.

Posterior Fossa Tumor.—(1) the ion-atlas relationship is frequently altered (ion higher than normal) due to an increase in the size of the posterior fossa and attributable to the effects of an expanding neoplasm. (2) Ventriculograms will usually show symmetrical dilatations of the lateral ventricles and possibly the third ventricle, whereas the fourth ventricle is rarely visualized. (3) Some of the cerebellar symptoms are unsteady gait and vertigo, ataxia, nystagmus, past pointing, and adiodokinesis. After the disease has progressed, hypotonia and stiffness of the neck may occur. This stiffness is due to herniation of the cerebellar tonsils. The head may be tilted to the side of the lesion, and the chin pointed to the opposite shoulder. (4) Compression of the brain stem produces signs of involvement of various cranial nerves. (5) Signs and symptoms of increased intracranial pressure are frequent.

The histologic varieties of subtentorial tumor most often encountered are astrocytoma and medulloblastoma.

Supratentorial Tumors—The signs are (a) those of increased intracranial pressure, some of which are described above, (b) focal signs, and (3) signs of involvement of adjacent structures.

Neoplasms of the Frontal Lobes—These are distinctly rare but when they do occur produce mental changes such as apathy and untidiness, tremors and aphasia, all of which may be observed with cerebral hemisphere involvement. A ventriculogram will generally show relative or absolute enlargement of the opposite ventricle and narrowing of the ventricle on the affected side.

Cranio-pharyngioma—The most common tumor observed in the supratentorial area is craniopharyngioma (Rathke's pouch cyst, suprasellar cyst) (Fig 59). This is a cystic neoplasm resulting from failure of the evagination of the primitive oral cavity (stomodeum) to in-

distant one. Sometimes it confines itself, fortunately, to one region and there "burns out." In some cases symptoms may be quite painful and disabling, yet roentgenographic signs may be quite tardy in appearance. In other cases there are few or no symptoms except stiffness. Patients may then long delay consulting a physician and, when they do consult him, he is surprised by the notable roentgenographic changes present. Such a patient may find it difficult to realize that he has already had the disease for months or years.

Among the 1,035 Clinic cases, symptoms first affected the lower part of the back (sacro-iliac or lumbar regions) in 35 per cent, hips



Fig. 150—Man, aged thirty-one years. Although he had had low back pain (gluteal, sacro-iliac and sciatic) for nine years, roentgenograms revealed only moderate cloudiness of sacro-iliac joints and adjacent bone (bilateral sacro-iliitis). The sedimentation rate was 54 mm. in one hour (Westergren method).

in 12 per cent, sciatic region in 10 per cent, thoracic region in 6 per cent and neck and shoulders in 3 per cent, the initial symptoms were not well localized in 11 per cent, peripheral joints were first affected in 23 per cent.

The onset of the disease was "acute" in 14 per cent but insidious in 86 per cent.⁶⁴

The course was interrupted by exacerbations and remissions in about 70 per cent, it was progressive in about 30 per cent. This was true regardless of where the disease first started. Thus the initial

localization did not determine the subsequent course of the disease, the degree of severity, the prognosis or the ultimate degree of improvement

Despite its relative infrequency the disease in women progressed about the same as in men

7 How Long Does the Disease Generally Last?—It is impossible for us to answer this question precisely. We do not know of any acceptable statistics on this point. When a patient's symptoms become insignificant or relatively mild he ceases to see his physician. Only those patients still having trouble consult their physicians and it is only with such patients that most statistics have dealt.

The experiences of 1,018 (of the 1,035) spondylitic patients seen at the Clinic have been of interest. Among them symptoms of the disease had been present for less than five years in 30 per cent, between five and nine years in 34 per cent, between ten and fourteen years in 20 per cent, between fifteen and nineteen years in 9 per cent and for twenty years or more in 7 per cent. Although thirty-four patients claimed to have had symptoms for twenty-five to fifty years, the majority had had symptoms for five to fifteen years.

In summary, no prediction can be made in a given case as to how soon the disease may become inactive, relief of symptoms may be soon or long delayed. The disease may become inactive for months or years and then be reactivated for a while. Perhaps an "intelligent guess" would be that most patients can expect their disease to become relatively inactive after an average of about ten years. This is certainly not a glowing prospect and indicates the "seriousness" of the disease.

8 What Are the Chances That the Disease Will "Spread" to Peripheral Joints (Other than Hips)?—It has been stated that peripheral joints, other than hips, are rarely affected in rheumatoid spondylitis^{13, 15, 16, 35, 40}. Among eighty-four spondylitic male patients Swain noted involvement of "small joints" in only 6 per cent. Higher incidences have been reported: peripheral joints were (or had been) affected in 20 per cent of Hare's cases and in 23 per cent of those of Boland and Present.

Our own experiences indicate an even more frequent involvement of peripheral joints. In about a fourth of cases in which rheumatoid spondylitis develops symptoms will develop in peripheral joints (more often in lower than upper extremities) even before the onset of the main (spinal) disease. But only half of the patients so affected will develop demonstrable residual involvement of peripheral joints, in the others symptoms in peripheral joints will be transient and will disappear without significant residues.

After the onset of spinal symptoms, involvement of peripheral joints may be anticipated in slightly more than a fourth of the cases. In a little more than half of these, chronic residual involvement will

occur, while in the remainder, the peripheral joint symptoms again will be only transient. The occurrence of symptoms referable to peripheral joints prior to the onset of spinal symptoms does not predispose to further involvement of peripheral joints later in the course of the disease.

In summary, of 100 spondylitic patients about 50 per cent will never develop any symptoms in peripheral joints. About 23 per cent will develop transitory involvement of peripheral joints (12 per cent before and 11 per cent after the onset of spinal symptoms). About 27 per cent will develop some chronic disability in peripheral joints (11 per cent before and 16 per cent after onset of spinal symptoms), but in at least a third of these cases only one joint will be chronically affected.

9 How Often Do Hip Joints Become Notably Affected?—Since significant spinal flexion is usually preventable and since peripheral joints become chronically disabled only in the minority of cases, the outlook for the spondylitic patient and his chances of escaping economic disability are good so long as the hips do not become notably involved. Significant deformity of hips constitutes the greatest hazard.

Many patients complain of pain about the "hips" but they are referring to their buttocks, sacro-iliac regions, thighs, and so forth, and not to the hip joints. Others have muscular soreness and stiffness about the hips but no actual articular involvement. Significant involvement of hip joints reportedly occurs in from 15 to 60 per cent of spondylitic patients.⁶⁴ In the Clinic series obvious arthritis of hips occurred in about 28 per cent of cases, in three fourths of which both hips were affected. In all of these cases the hip disease was notable and presented an important disability.

10 Are There Any Special Features of the Affected Peripheral Joints?—Three features will be mentioned.

(a) When peripheral joints (other than hips) do become affected in rheumatoid spondylitis they are generally affected less symmetrically than in patients with typical rheumatoid arthritis.

(b) As stated, in about half of the cases the affected peripheral joints clear up without apparent residual damage.

(c) Histologic studies made on the available material from involved peripheral joints including hips (six hips, three knees, one shoulder) in the Clinic's cases revealed cellular reactions in synovia indistinguishable from those seen in cases of classic rheumatoid arthritis without spondylitis.⁶⁴

11 What Complications or Unusual Features May Arise during the Course of Rheumatoid Spondylitis?—In certain cases of "spondylitis ankylopoietica" Edstrom noted the occurrence of pleuritis, endocarditis, iritis or subcutaneous nodules—lesions in mesenchymal tissues. Because these complications are similar to those of classic

rheumatoid arthritis he concluded that the two diseases are closely related if not identical. According to Herrick and Tyson, subcutaneous fibrous nodules do not occur in rheumatoid spondylitis without peripheral involvement.

Iritis reportedly occurs as a complication in about 3 to 5 per cent of cases of peripheral rheumatoid arthritis⁶⁴ but it is reported as occurring in from 7 to 40 per cent of cases of rheumatoid spondylitis^{28, 64}. Of the 1,035 spondylitic patients seen at the Clinic iritis affected 11.6 per cent (120 patients). In about half of those affected the iritis was recurrent, the others experienced only one episode of iritis.

Iritis generally occurs during the course and development of the spondylitis but it occasionally precedes the spinal symptoms by one or several years; occasionally it occurs simultaneously with the onset of spinal symptoms.

As has been reported elsewhere by one of us⁴⁵ pregnancy may provide notable or complete temporary relief for women who have rheumatoid arthritis or spondylitis. Such relief was experienced by 32 per cent of nineteen spondylitic women who became pregnant.⁶⁴

ROENTGENOGRAPHIC CHANGES

12. What Roentgenographic Changes Occur?—As each region is involved the following changes may progressively occur therein.

Sacro-iliac Joints—The changes in these joints occur roughly in three stages.^{8, 30} In the first stage there occurs blurring of joint space with indistinct or broken margins. In the second stage pyknotic formation produces a mottled appearance with spotty osteoporosis (decalcification) or increased density (hypercalcification), or both, of juxta-articular bone. The marginal decalcification may produce pseudo-widening of the articular space. The third stage is characterized by disappearance of articular space, fibrillary ossification with regions of osteosclerosis and finally ankylosis.

Apophyseal Joints—Changes therein are difficult to visualize, to demonstrate them, projections from several angles may be required. Early changes comprise merely blurring or haziness, producing an indistinct articular outline. Later there occur stippled decalcification or sclerosis or both, sometimes cystic rarefaction of facets and various degrees of articular destruction.

Ligaments—The anterior common, lateral and posterior longitudinal ligaments and ligamenta flava become calcified and ossified. As these processes occur, one notes fine penciled lines, later more sharply defined shadows and finally extensive "bambooning" as the syndesmo-phytes unite to form the "bamboo spine" (fig. 151).

Vertebral Bodies—These remain unchanged except for osteoporosis from demineralization.

Intervertebral Disks—Usually these are not affected.

13 How Closely Can the Roentgenographic Changes Be Correlated with the Symptoms and Clinical Course of the Disease?—There are so many variations in the severity and course of the disease and in the reaction (and speed of reaction) of individual patients to it, that no precisely defined anatomic, clinical or radiologic stages can



Fig 151—Man, aged twenty-nine, who had had symptoms of rheumatoid spondylitis for five years. Roentgenograms show bilateral destructive sacro-iliac arthritis and calcification of the ligaments between the twelfth thoracic and the first lumbar vertebra, a common location for early calcification of the ligaments. A small globule of iodized oil is seen in the subarachnoid space, the result of spinozography performed elsewhere.

be established. Only in a general way can roentgenographic changes be correlated with the symptoms and physical signs of the disease.

When the disease follows its usual course, in the early stage one generally finds roentgenographic alterations in sacro-iliac joints but not yet in apophyseal joints or ligaments. Sometimes the sacro-iliac changes develop rapidly and "outrun" the symptoms, sometimes they appear very slowly with notable symptoms long present.

If the spread of the disease is an ascending one, as it usually is, the next general phase is featured by more progressive sacro-iliac changes and early alterations in apophyseal joints, the ligaments still appearing essentially normal in roentgenograms. In a further phase one may note advanced sacro-iliac changes (perhaps complete ankylosis), moderately advanced apophyseal changes and early evidences of spotty ligamentous calcification. But sometimes ligamentous calcification proceeds apace and is notably present fairly early in the general course of *symptoms*.

If the disease progresses to the "final phase" when the spinal column is stiffened and probably becoming rather painless, sacro-iliac joints are usually ankylosed, some apophyseal joints are notably involved or destroyed, although others may still be apparently unaffected roentgenographically, and extensive ligamentous calcification has produced the "bamboo spine."

14 Are the Sacro-iliac Joints Always Affected in Rheumatoid Spondylitis?—The answer is "No, not always, but almost always"

Some physicians have insisted that the sacro-iliac joints are always affected sooner or later, generally early. Indeed Scott^{69, 70, 72} concluded that a "sacro-iliac infection" is long symptomless and generally starts several years prior to symptoms in the sacro-iliac joints themselves or elsewhere in the back, and that spinal symptoms do not begin until *ankylosis* of sacro-iliac joints has begun.

But other rheumatologists have disagreed with this view, and Buckley,¹⁵⁻¹⁷ Gordon, and Forester have reported cases of undoubted rheumatoid spondylitis in which sacro-iliac joints were still normal roentgenographically. Key examined two skeletons with typical ankylosing spondylitis in which the sacro-iliac joints were not involved. The upper part of the spinal column may be clinically and roentgenographically affected but sacro-iliac joints may still be normal (figs. 152 and 153).¹⁵ However, sacro-iliac joints were apparently unaffected (that is, normal roentgenographically) in only two of Forester's 153 cases. Sacro-iliac changes were present in every one of the 100 cases of Boland and Present, probably because they admittedly "hesitated to make an unequivocal diagnosis" when these joints appeared normal.

Among the Clinic's 1,035 cases, sacro-iliac joints were *bilaterally* normal roentgenographically in only nine cases, in these cases symptoms and signs elsewhere in the spinal column had been present for as long as twenty years. In six additional cases *unilateral* sacro-iliac arthritis was present.²⁵ It has been claimed that unilateral sacro-ileitis (without other roentgenographic signs of rheumatoid spondylitis) should suggest the presence of a specific infectious arthritis, especially tuberculosis.^{26, 70} Unilateral sacro-ileitis can occur occasionally with the later development of typical rheumatoid spondylitis.

So commonly and early are sacro-iliac joints affected in this disease that, even though the disease stops there or remains localized there for years, one must consider that an "abortive" rheumatoid spondyli-



Fig 152—Man, aged fifty-seven years, who had had spinal symptoms for twenty-five years and involvement of peripheral joints for ten years. Note the extensive calcification of ligaments with ankylosis of vertebrae and moderate kyphosis.

tis is present. The vague diagnosis "sacro-iliac arthritis" used to be made commonly. In the light of current concepts a useful maxim is "Bilateral sacro-ileitis means (the first stage of) rheumatoid spondylitis" (fig 154).

RHEUMATOID SPONDYLITIS

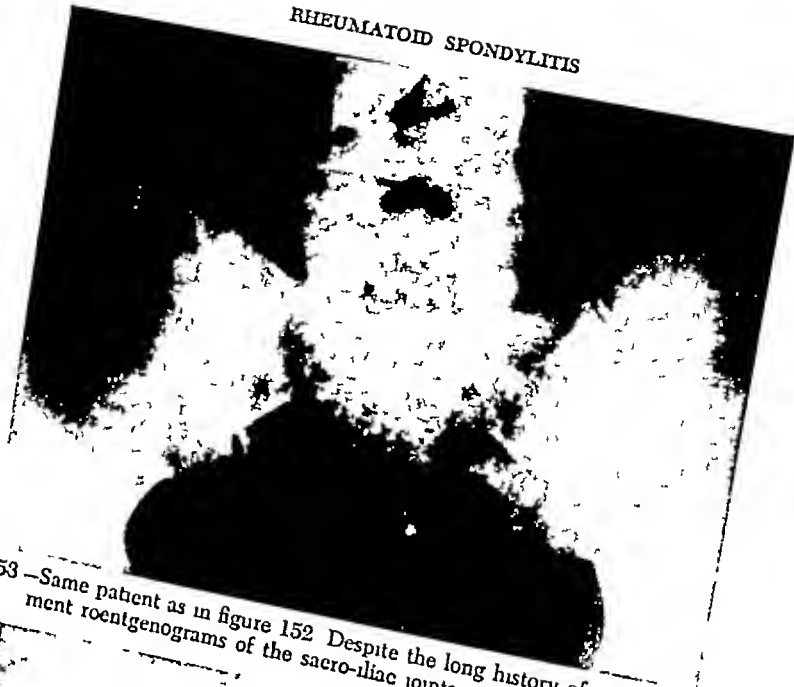


Fig 153—Same patient as in figure 152 Despite the long history of spinal involvement roentgenograms of the sacro-iliac joints were still normal.



Fig 154—Man, aged forty two years, who had had spinal symptoms for twenty-one years, after which roentgenograms of the spinal column were still negative except for bilateral destructive sacro-iliac arthritis

15 By the Time the Patient First Consults a Physician are Roentgenographic Changes Likely to be Present?—When the patient first consults his family physician for the early intermittent symptoms of soreness and stiffness, roentgenograms may be negative because the articular (synovial) involvement in sacro-iliac or apophyseal joints has not yet produced sufficient involvement of cartilage or subchondral bone to be detectable. But some patients who have only stiffness and little or no pain delay their first visit to the family physician until roentgenographic changes are already discoverable and are sometimes surprisingly advanced.

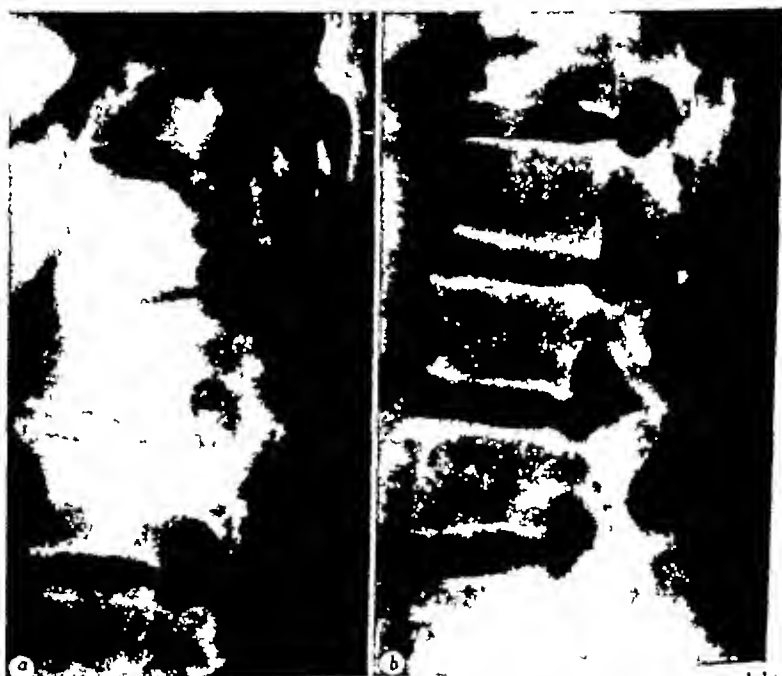


Fig 155—Syndesmophytes (calcified ligaments) of rheumatoid spondylitis (a) compared with osteophytes of spinal osteo-arthritis (b), lateral views of lumbar regions

By the time patients consult a rheumatologist or other specialist roentgenographic changes, at least in the sacro-iliac joints, have generally, though not always, occurred.⁷³

16 How Do the Roentgenographic Changes of Rheumatoid Spondylitis Differ from Those of Spinal Osteo-arthritis?—First of all the sacro-iliac joints in spinal osteo-arthritis are generally essentially normal or reveal only slight marginalipping. Roentgenograms in spinal osteo-arthritis may reveal the following: early flattening of the margins of the vertebral bodies, later the formation of osteophytes.

marginal exostoses. The vertebral bodies, but especially the intervertebral disks, are often narrowed in osteo-arthritis, features not characteristic of rheumatoid spondylitis.

Calcific deposits in spinal ligaments are not pathognomonic of, or confined to, rheumatoid spondylitis. Small scattered regions of calcification may occur in spinal osteo-arthritis with osteophytic lipping but there is no tendency for them to coalesce or form ankyloses.

When syndesmophytes are few, scattered or present singly in rheumatoid spondylitis, they are sometimes mistaken for osteophytes. Syndesmophytes, being calcific deposits in paraspinal ligaments, of necessity appear in the position of the ligaments, thus they "droop" or rise rather perpendicularly from the adjacent vertebral body (figs

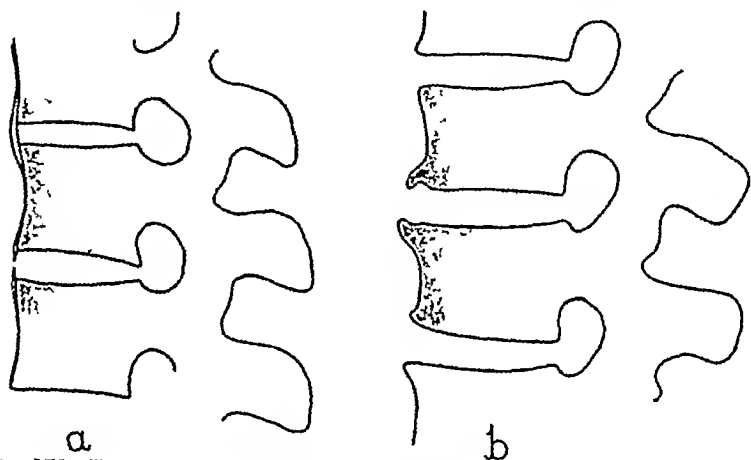


Fig. 158.—Diagrammatic representation of figure 155, *a* and *b*, lateral views of lumbar regions

155 and 158) Osteophytes, not so strictly confined, generally grow laterally a little way and then may curve downward or upward.

A syndesmophyte can be differentiated easily from an osteophyte even from its beginning, according to Forestier. A syndesmophyte appears as a woolly shadow in the intervertebral space, in a few months there appears a rather clear-cut, dense, linear area of calcification without a cortex, which looks like a thin or thick comma on the vertebral body. An osteophyte has a thicker base, is covered with a cortex arising from that of the vertebral body and possesses a structure of cancellous bone like the vertebral body itself.

DIAGNOSIS

17 How Can One Diagnose Rheumatoid Spondylitis Early in Its Course?—An early diagnosis of rheumatoid spondylitis is generally based on the character and location of the stiffness and pain, the

volute. It often contains cholesterol crystals and calcium deposits in the cyst wall. Although the tumor is benign, its proximity to and anatomic association with important cerebral structures augurs for a generally unfavorable prognosis.

In such cases, too, location determines the clinical findings. Most craniopharyngiomas cause compression of the third ventricle with resulting hydrocephalus. Visual difficulties, resulting from pressure on the optic chiasm, are usually asymmetrical.

Defects in the visual fields, scotoma, hemianopsia and optic atrophy may also be present. If intracranial pressure is simultaneously asso-

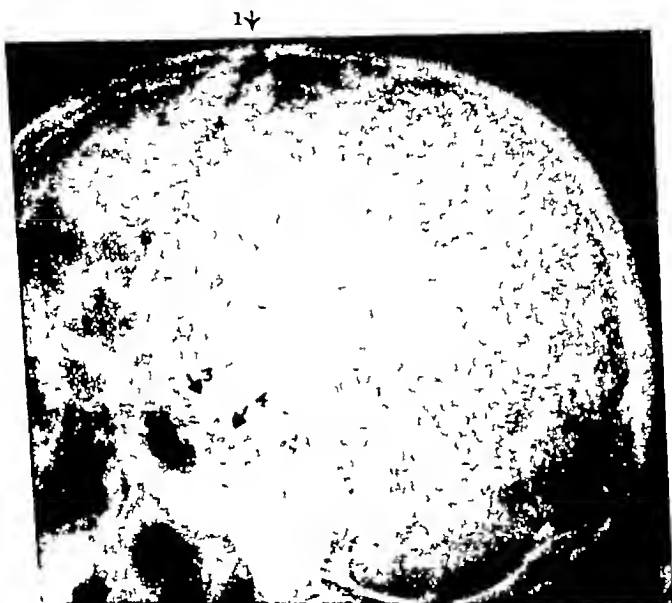


Fig. 59—Craniopharyngioma (J. G., male, aged 9 years). Roentgenogram shows (1) separation of sutures, (2) accentuation of digital markings, (3) crystalline shadows, (4) erosion of clinoid processes. The child survived four years following his first operation but succumbed after a recurrence.

ciated with optic chiasm involvement, the ocular symptoms will be many and varied. Rigidity or tremor may be present if the thalamus or the basal ganglia are involved. Hypothalamic and pituitary alterations may be evident. Almost all of such cases show somatic and metabolic changes and growth therefore may be retarded or accelerated. Pubertas praecox and infantilism have been observed and obesity and polydipsia are not infrequent manifestations.

Röntgenologically the skull shows separation of the sutures, increased digital markings, erosion or distortion of the clinoid processes and, occasionally, crystalline shadows in the suprasellar region.

presence of muscle spasm, flattening of the normal lumbar lordotic curve, limitation of forward bending, an elevated sedimentation rate, roentgenographic alterations in sacro-iliac joints or elsewhere, and perhaps also such constitutional reactions as loss of weight, mild secondary anemia and occasional slight fever.

The most useful single laboratory aid in the diagnosis of rheumatoid spondylitis consists in roentgenographic examination of sacro-iliac joints. Although there is an appreciable lag between the development of physical findings and roentgenographic alterations⁵ this lag is generally more than compensated for by the patient's tardiness in consulting a physician. Hence, even in fairly early cases roentgenograms generally already reveal sacro-iliac alterations.

Sedimentation rates are increased (more than 20 mm in 1 hour, Westergren method) in about 90+ per cent of cases of peripheral rheumatoid arthritis and in about 80 per cent of cases of rheumatoid spondylitis. In the Clinic's cases of spondylitis, rates were normal in 19 per cent, between 20 and 39 mm (1 hour) in 27 per cent, between 40 and 59 mm. in 28 per cent, between 60 and 79 mm in 14 per cent, between 80 and 99 mm in 8 per cent and 100 mm or more in 4 per cent. Thus rates were less than 60 mm in 74 per cent. It appears that rates are not elevated quite as often or as much in rheumatoid spondylitis as in rheumatoid arthritis.⁶ Although the sedimentation rate generally rises with increased activity of the disease, in the Clinic's series rates were elevated to more than 20 mm (1 hour) in only about 80 per cent of cases regardless of the duration or severity of the disease.

When roentgenograms are still negative, an elevated sedimentation rate is of particular significance, since rates are not elevated in simple muscular rheumatism (primary fibrositis) of the back or in uncomplicated osteo-arthritic spondylitis.

In the early stages of some cases roentgenograms are negative but sedimentation rates are elevated, in other cases the reverse is true. When the symptoms and signs mentioned previously are as yet unaccompanied by abnormalities in roentgenograms or sedimentation rates, only a tentative diagnosis should be made.

These and other points useful for the early diagnosis of rheumatoid spondylitis have been stated by Boland and Present in the form of eleven useful maxims worth remembering.

1. Suspect rheumatoid spondylitis when a young man complains of chronic recurrent or persistent low back aching and stiffness, with or without catching pains, especially if the sedimentation rate is elevated.

2. Suspect rheumatoid spondylitis in the young man who complains of such vague symptoms as a "tired feeling" in the lower part of the back on standing and walking, persistent low back soreness, silent restriction of back motion, or infrequent sharp pains in the buttocks, hips or lower part of the back, especially if accompanied by an elevated sedimentation rate or general constitutional symptoms.

3 Suspect rheumatoid spondylitis in all cases of sciatica in young men, particularly if recurrent or alternating from side to side or associated with aching and stiffness of the lower back.

4 Suspect rheumatoid spondylitis in patients with thoracic girdle pains, especially if accompanied by symptoms in the lower part of the back

5 Suspect rheumatoid spondylitis when persistent back symptoms develop in a patient with peripheral rheumatoid arthritis

6 In the absence of roentgenographic evidence of sacroiliac involvement an unequivocal diagnosis of rheumatoid spondylitis should not be made unless characteristic changes are present in the apophysial joints

7 Remember that characteristic x-ray changes in the sacroiliac or apophysial joints may not develop for months after the onset of symptoms Do not eliminate the possibility of rheumatoid spondylitis on negative x-rays alone unless persistent symptoms have existed for at least three years

8 Definite bilateral destructive and/or sclerotic changes in the sacroiliac joints, noted roentgenographically, almost invariably indicate rheumatoid spondylitis

9 Be cautious in making a diagnosis of rheumatoid spondylitis with unilateral sacroiliac involvement unless other characteristics of the disease are present or unless peripheral rheumatoid arthritis coexists Persistent unilateral sacro-ileitis may be due to tuberculosis

10 Calcification of the paravertebral ligaments may result from several causes and in itself is not sufficient evidence for the diagnosis of rheumatoid spondylitis, changes in the apophysial and/or sacroiliac joints must also be present

11 Remember that the sedimentation rate may be normal in 15 to 20 per cent of cases with active disease and that constitutional symptoms are usually milder than in rheumatoid arthritis involving peripheral joints

18 From What Common Conditions Must Rheumatoid Spondylitis Be Differentiated?—From osteo-arthritic spondylitis, primary intramuscular fibrositis, "psychogenic rheumatism" of the back, ruptured intervertebral disks and the symptoms produced by herniations of subfascial fat

A careful analysis of symptoms and signs supplemented by roentgenograms provides the chief methods of differentiation Roentgenograms and sedimentation rates are normal in cases of primary fibrositis, psychogenic rheumatism and subfascial fat hernias

Patients who have osteo-arthritic spondylitis are female as often as male and are usually considerably older (aged 45 years or more) when first affected than those who have rheumatoid spondylitis, spinal stiffness, muscular spasm and limited motion are generally much less severe in spinal osteo-arthritis than in rheumatoid spondylitis The differences between syndesmophytes and osteophytes have been described The palpation of tender herniations of fat^{24, 25, 50} or a knowledge of the clinical features of psychogenic rheumatism^{7, 41, 47} will serve to distinguish these conditions readily from rheumatoid spondylitis.

19 Are Analyses of Cerebrospinal Fluid of Diagnostic Value in Rheumatoid Spondylitis?—In general, no The manometric pressure, cell counts and concentrations of sugar in cerebrospinal fluid are nor-

mal, colloidal gold reactions are generally normal⁵⁷ But in about 40 per cent of cases of rheumatoid spondylitis the total protein content of lumbar spinal fluid is moderately increased, between 45 and 105 mg per 100 c c⁹ The lumbar fluid protein concentration is increased sometimes in peripheral rheumatoid arthritis without spondylitis (in about 7 per cent of cases), more often in rheumatoid spondylitis alone (in about 33 per cent of cases), and most often (in 59 per cent of cases) when rheumatoid arthritis of both the spinal column and peripheral joints is present In rheumatoid spondylitis the increase is related to the severity of the disease but not to its duration or amount of involvement of the spinal column

The increase of spinal fluid protein in rheumatoid spondylitis is of about the same order as that in most cases of ruptured intervertebral disks but it is usually much less than in cases of partial or complete subarachnoid block such as may result from a tumor of the spinal cord Hence, if the lumbar fluid protein in any given case is increased notably above 100 mm per 100 c c, some cause other than rheumatoid spondylitis should be sought even though spondylitis is present

TREATMENT

20 What General Principles Govern Treatment?—The different forms of treatment recommended hereinafter are designed to accomplish three chief purposes (1) to relieve pain, (2) to prevent spinal deformity and (3) to attempt to shorten the course of the disease, to induce a state of "cure" or clinical inactivity The situation would be ideal were the physician able to limit the disease to the sacro-iliac joints and to obtain fusion therein as soon as possible Unfortunately this is not yet possible, as there is no known specific or rapid cure for the disease and no certain means of controlling it Nevertheless, treatment instituted early and continued faithfully will do much to relieve pain and prevent significant deformities

21 What Appears Currently to Be the Best Treatment for Rheumatoid Spondylitis?—Answer a combination of (a) roentgen therapy, (b) physical therapy including deep breathing and postural exercises, and (c) the proper use of bed and bedding during sleep

(a) *Roentgen Therapy*—For fifty years various programs of roentgen therapy have been used for rheumatoid spondylitis with no general unanimity of opinion as to their value^{33, 53} Four main programs have been employed (1) the use of penetrating rays (180 to 200 kv) recommended by the majority,⁵³ (2) the use of softer rays (80 to 120 kv) which are absorbed and are nonpenetrating, (3) the use of rays of medium length (130 to 140 kv),^{63, 71} these three types being applied to joints, and (4) irradiation of lumbar and cervical sympathetic ganglia

"Deep (short wave or very penetrating) roentgen therapy" has recently been preferred by some^{39, 48, 54} Others, notably Scott,^{68, 69} considered deep or short wave-length roentgen rays "absolutely contraindicated" but regarded wide field radiation with rays of medium length (130 to 140 kv) as highly beneficial in rheumatoid spondylitis

Currently the technic of Freyberg and his colleagues is in favor In 1941 Smyth, Freyberg and Lampe reported excellent results in the treatment of fifty-two patients who had rheumatoid spondylitis; notable subjective improvement was obtained in 72 per cent, notable objective improvement in 50 per cent. To rule out a psychic effect control patients were placed on the treatment table as for roentgen therapy but, without their knowledge, the rays were blocked by lead screens From such "placebo therapy" no significant results were obtained

This work was recently confirmed and extended by Smith, Boland, Shebesta and Hench, who treated seventy-five spondylitic patients Roentgen therapy was given to twenty-five patients with notable objective improvement in 68 per cent "Placebo therapy" similar to that used by Smyth, Freyberg and Lampe was given to twenty-five patients with notable objective improvement in only 8 per cent. Deep breathing and postural exercises were given to twenty-five patients with notable objective improvement in 40 per cent Best results were obtained when roentgen therapy was combined with deep breathing and postural exercises

For the details of these treatments the original references should be consulted In general the spinal column was divided into four or five areas or "portals," each portal receiving a total of 600 r (200 r on three separated days of treatment) A second and possibly a third series of treatments were given four to six weeks apart Relief was often noted within a week or so after the first treatments and resulted apparently from lessening of muscle spasm and pain Recently Freyberg,³³ to reduce the incidence of "roentgen sickness," recommended an alternate scheme using lower voltages (about 140 kv) wider and fewer portals and smaller doses of the rays (100 to 150 r \times 3)

(b) *Postural and Deep-Breathing Exercises*—These should be done two or three times daily for periods of five to ten minutes each.

(c) *Night Posture*—A piece of board under the entire mattress tends to prevent sagging of the bed and curvature of the upper part of the spinal column A small soft pillow under the lumbar region will help to maintain the normal lumbar curve Patients should lie in bed on their backs using preferably no pillow or, if a pillow is necessary, only one small pillow under the head.

22. *How Much Physical Activity and Exercise Should the Spondylitic Patient Be Allowed?*—Spondylitic patients should follow the same "rules of exercise" which apply to patients who have peripheral

rheumatoid arthritis⁴³ They must avoid whatever type or amount of exercise is followed later in the day or the next day by an increase of symptoms or disability. In particular they should avoid activities which produce sudden jars or torsion, for example, golf, horseback riding or tennis Swimming in relatively warm water is usually an acceptable recreation A generous amount of rest is desirable but excesses of rest should be avoided as they predispose to unnecessary degrees of spinal and thoracic rigidity

23 How Can Spinal Deformity Be Prevented?—Minimal deformities and certain limitations of spinal motion are unavoidable but significant spinal *curvatures* are preventable. Notable spinal deformities generally represent inadequate or improper treatment The patient should measure his height at least once monthly (for example, on the first day of each month) and record it If he is carrying out his treatment half-heartedly and is losing height significantly ($\frac{1}{4}$ to $\frac{1}{2}$ inch [0.64 to 1.3 cm] or more) he should vigorously apply the measures outlined in the answer to question 21. If despite this, the spinal curvature persists, other measures are in order more intensive physical therapy (heat and massage) and perhaps a course of mild fever therapy using hot baths, or typhoid vaccine reactions⁴⁶ to relieve muscle spasm, generally also the use of a Taylor brace In severe cases a plaster jacket or a plaster half-shell or hyperextension frame by night may be required⁷⁰

24 Is the Use of Gold Salts of Value?—Although chrysotherapy in rheumatoid spondylitis has been considered of value by some physicians, others have labeled their results "disappointing,"¹⁴ ^{51, 52} "useless,"⁴ "rarely good"⁷⁴ or "poor"^{20, 37}

25 Will Removal of Infected Foci or the Use of Streptococcal Vaccines Alter the Course of the Disease?—We have no definite knowledge that such measures alter the course of the disease appreciably Obviously infected foci should be removed for purposes of improving general health but not as a cure of the spondylitis The use of streptococcal vaccines is diminishing notably Physicians sometimes publish their recommendations of these measures but generally fail to give statistical results for treated patients or for controls not so treated.

26 "Doctor, Is There Any Medicine That Will Remove These Lime Deposits from My Spine?"—Answer No safe medicines Some nostrums are advertised for this purpose Most of them are probably harmless but they are useless and ineffective Those few which are capable of mobilizing calcium deposits probably contain concentrated vitamin D or parathormone, in which case they are potentially dangerous, as such preparations make no distinction between the new ectopic calcium deposits in ligaments and the normal calcium in bones. Since they act alike "on the just and on the unjust calcium," their

persistent use may lead to severe osteoporosis, spontaneous fractures, cysts in bones, ectopic calcium deposits in kidneys and elsewhere, perhaps also severe or fatal nephritis, such as we and others are now encountering fairly frequently in cases of vitamin D intoxication in patients with peripheral and spinal rheumatoid arthritis^{9, 31, 75}

27 **How about Climate for Rheumatoid Spondylitis?**—There is no region where the climate is beneficial to all patients who have rheumatoid arthritis or spondylitis. Some patients feel better wintering in dry Arizona or New Mexico despite the rather notable shifts in temperature between the winter noons and nights. Some patients feel better on the warm California or Florida coasts despite the humidity. Others actually feel better wintering in cold dry parts of New England than they do on a humid summer day in, for example, Chicago.

The reason for these diverse responses, aside from the factor of rest, incident to a vacation, is that climate or weather is a composite of many factors, among them temperature, humidity, barometric pressure and atmospheric electricity. Certain rheumatic patients seem to react badly to alterations of temperature but not particularly to alterations of humidity or barometric pressure. Other patients do not seem to mind temperature changes but feel best where the barometer is steady and the humidity low. Others react in varying degrees to all of these factors. Hence, physicians cannot advise their rheumatoid patients as to the optimal individual climate unless the patient himself knows how he reacts to each of these factors. The patient's own experiences are the best guide.

In any event a relatively short stay of a few weeks or months or for a "season" in any given climate will rarely cure the disease, although the patient often feels better temporarily. Because of economic necessity most spondylitic patients must cope with their disease at home with the means at hand, relying on the measures outlined and making their own microclimate by appropriate heating, controlled humidity and clothing.

28 **Are Any of the Newer Therapeutic Agents of Value: Penicillin, Streptomycin, Bogomoletz' Antireticular Cytotoxic Serum, Neostigmine or Physostigmine?**—Penicillin was given to three small groups of patients who had peripheral rheumatoid arthritis, three patients had spinal involvement but were not benefited.^{10, 23, 28} In view of the negative results one would not expect penicillin to affect rheumatoid spondylitis.

The effect of streptomycin on rheumatoid spondylitis has not yet been reported. Preliminary results indicate that it is ineffective against peripheral rheumatoid arthritis.²³

The administration of Bogomoletz' antireticular cytotoxic serum was followed by "definite improvement" in one of two cases in which "spondylitis ankylopoietica" was treated by Bach.² However, the pre-

liminary results of Freyberg,³⁴ who administered the serum to about thirty patients who had peripheral or spinal rheumatoid arthritis, were disappointing

The use of neostigmine bromide or of physostigmine salicylate was recently recommended to relieve muscle spasms in cases of rheumatoid arthritis and spondylitis^{21, 52, 81} However, several experienced rheumatologists have recently been disappointed with this remedy⁴² and Balboni, Hollander and Kydd, who used neostigmine in twenty-three cases of rheumatoid arthritis including ten with spondylitis, noted no significant relaxation of muscular spasms and concluded that its use in such cases is unjustified

29 Do Patients Who Have Rheumatoid Spondylitis Require Narcotics?—In general, no During acute exacerbations of rheumatoid spondylitis when muscular spasms are producing rather severe pains, the temporary supplemental use of codeine for a few days may be justified.

When a patient supposed to have spondylitis develops *chronic* distress sufficient to require narcotics a review of the case is in order. A useful maxim to remember is that "rheumatism requiring narcotics is *not* rheumatism" Patients who have chronic spinal symptoms actually painful enough to warrant the use of narcotics are generally suffering from metastatic malignant lesions of the spinal column^{43 67} They may also, incidentally, have spinal osteo-arthritis

30 What Are the Results of Treatment?—Most physicians who have studied and treated large numbers of patients who had rheumatoid spondylitis have failed to report statistically the results of treatment The widely differing natural course of the disease in individual cases and the varying responses of patients to the remedies used make such an assessment most difficult It is not easy to determine how effective any one measure is or to decide whether a remission resulted from, or merely followed, a given remedy

Without attempting to evaluate treatments per se, Polley⁶¹ merely reported the state of affairs uncovered by a follow-up study. Of 617 questionnaires returned the results were reported as follows 53 per cent of these 617 patients were "improved" and of this group 70 per cent were "working full time," generally and wisely at nontraumatizing occupations, 21 per cent considered their condition "unchanged"—no better but at least no worse, in 19 per cent the condition was "worse" Death had occurred in 2 per cent of the cases, causes of death being miscellaneous and not obviously related to the spondylitis

These figures have a familiar ring, reminding us of "the inevitable 65 per cent" of rheumatoid patients who "improve" under this or that remedy But one must not belittle the importance of such figures, rather one should take heart from the repeated demonstration that, regardless of the reasons therefore, about two thirds of patients with

rheumatoid spondylitis or arthritis get better, sometimes slowly, sometimes fairly rapidly

Evaluating roentgen therapy Freyberg and his colleagues,^{33, 77} Hernaman-Johnson and others have reported frequent prolonged and complete remissions (a better term than "cure") resulting promptly therefrom. We certainly do need remedies superior to those now available. But until they are developed, the use of the measures discussed herein may provide much comfort to the numerous victims of this strange disease.

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MANAGEMENT OF INTRACRANIAL TUMORS—It is important to investigate all cases of intracranial tumors surgically. Small hemangiomas, meningiomas, colloid cysts and other benign or completely removable neoplasms have been encountered unexpectedly and treated successfully. Irradiation is reserved for the malignant varieties and certain nonmalignant types.

SPINAL CORD TUMORS

These are very rare in children. Common symptoms presented by some of them are weakness, spasticity and sensory changes, usually below the segment of the tumor.

The neoplasm must be differentiated from other spinal cord diseases. Roentgenography is of considerable diagnostic value in many cases.

TUMORS OF PERIPHERAL NERVES

These tumors are discussed under the general heading of tumors of the soft somatic tissues.

TUMORS OF THE SYMPATHETIC NERVOUS SYSTEM

The sympathetic neuroblast produces neuroblastoma and its more mature counterpart chromaffinoma (pheochromocytoma), both of which are malignant neoplasms—and ganglioneuroma, which is essentially a benign neoplasm.

Neuroblastoma (Fig. 60)—This is one of the more common malignant tumors observed in childhood, occurring in our experience from the first to the sixth year. It may arise from any part of the sympathetic nervous system. Some neuroblastomas arise in peripheral nerve areas as well as intracranially, but it is questionable whether these are related to the usual type of neuroblastoma.

The commonest primary site for this tumor is the adrenal medulla. The celiac plexus and thoracic sympathetics are also relatively frequent primary sites.

The primary tumor may be small, especially when it occurs in the adrenal medulla, although metastasis in the lymph nodes or skull may be the first evidence of disease.

It is to be differentiated from intra-abdominal and intrathoracic masses as well as lymph node enlargements from various causes. Many of these tumors bleed easily. Hemorrhage is particularly prone to occur about the orbit, in the middle ear, and in the peritoneal cavity, from tumor adjacent to these structures. The diagnosis is definitely established by biopsy.

MANAGEMENT—Surgical excision is indicated if the case is operable. Some varieties will respond to irradiation.

Ganglioneuroma.—This is a tumor which may occur in the run-around child and is diagnosed by the presence of a mass, sometimes of

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CARE OF THE PATIENT WHO HAS MYASTHENIA GRAVIS

L M EAGON

IN this discussion I aim to present the practical aspects of caring for the patient who has myasthenia gravis. I hope that it will be of value to the practitioner who, although lacking in experience with this disease, is called on to manage a myasthenic patient.

In such a discussion, with emphasis on practicality and with no intention of presenting an exhaustive treatise on any particular phase of treatment, it is difficult to give detailed credit to those who have contributed significantly to the present program of management. Certainly, not the least important of these contributors have been my colleagues in the Department of Neurology and Psychiatry of the Clinic and Dr. Walter Boothby, whose interest in myasthenia gravis attracted an unusually large number of patients to him in the previous decade.

The discoveries of two women have been outstanding. Dr. Harriet Edgeworth was the first person to find any significantly beneficial treatment, that is, ephedrine. Dr. Mary Walker discovered that neostigmine (prostigmine) is beneficial in myasthenia gravis. Up to the present time it is the most effective medicine available for relief of symptoms. The contributions of Viets, often in collaboration with Schwab, are most important in setting the tempo for the use of adequate amounts of neostigmine in this disease.

In the development of thymectomy as a treatment of myasthenia gravis I must mention Weigert, who first called attention to the association of myasthenia gravis and a tumor in the anterior mediastinum, and to the pathologists, notably Bell, Norris and Miller, whose studies established the relationship between myasthenia gravis and the thymus. Blalock and his collaborators, who reported the first strikingly successful results for thymectomy, are responsible for the keen interest now being displayed in the surgical treatment of myasthenia gravis. My personal knowledge of this aspect of the problem would not have been possible except for the co-operation of many colleagues, particularly Dr. O. T. Clagett in thoracic surgery, Dr. J. R. McDonald in pathology and Dr. C. A. Good in roentgenology. The following sections describe the procedures that my colleagues and I have found valuable in the treatment of myasthenia gravis.

INTRODUCTORY DISCUSSION WITH THE PATIENT

When the diagnosis of myasthenia gravis has been established we begin treatment. Naturally, the patient is concerned about himself and his disease, and we have found that a frank discussion of the problem

of myasthenia is a valuable prologue to the presentation of the more specific details of treatment

In our first interview with the patient after the diagnosis of myasthenia gravis has been established, we attempt to answer the questions which we have found by experience he is most likely to ask. They include "What is it?", "What causes it?", "Can it be cured?", "What shall I do about it?", and "Shall I get worse?"

We have found that such a discussion is frequently reassuring. In spite of the fact that we cannot tell the patient the ultimate cause of the disease nor promise a cure, he is often pleased to learn that he has better than a fighting chance. Occasionally, the patient has been misinformed about his disease and is pleased to learn that in all probability he will not "die within two years" and possibly may not "have to take neostigmine as long as he lives." He is pleased to learn that more than half the patients who have myasthenia gravis can lead relatively normal lives with modern treatment and that approximately 10 per cent have the disease in such mild form that although they are annoyed by it their usual activities—often for many years—need not be restricted. He is told that satisfactory remissions occur frequently and at times persist for many years. He learns that one patient after having symptoms for three years experienced a complete remission lasting twenty-nine years, that another has had a complete remission of symptoms for twenty-five years and that this may possibly represent a spontaneous cure of the disease. He learns that the disease need not always be serious, since two patients in our group had had the disease for more than twenty years before the diagnosis was made and consequently got along fairly well without any treatment.

There are other facts about myasthenia gravis that tend to allay the pessimism of the patient. Myasthenia gravis is not contagious and probably not hereditary. At least, familial occurrence of the disease is extremely rare. My colleagues and I know of only one case in which the child of a myasthenic mother had the disease. We have observed it only once in twins. Only one of our patients has reason to suspect that a parent, her mother, had myasthenia gravis.

Although disappointed to learn that neostigmine and ephedrine do not cure the disease, the patient is pleased to learn that the medical profession considers it a disease which may some day, perhaps soon, be curable. Particularly, if he himself has associated hyperthyroidism, he is made hopeful by knowledge that treatment of the hyperthyroidism may result in a remission, perhaps cure, of the associated myasthenia gravis. (At the time when this paper was written, five years after the patient reported by Kowallis, Haines and Pemberton had undergone subtotal thyroidectomy, she was in good health.) Although the experimental nature of thymectomy in the treatment of myasthenia gravis is explained carefully, knowledge that it may eventually prove

to be helpful in influencing beneficially the fundamental course of the patient's disease is gratifying to him.

If necessary, undue optimism on the part of the patient can be tempered by knowledge that almost half of the patients must restrict their recreational or occupational activities or both to varying degrees. Furthermore, in any given case the physician cannot predict with certainty what the course may be.

After this introductory discussion has taken place, my colleagues and I inform the patient that no matter what attempts are to be made to cure or at least alleviate his disease it will be necessary for him to have symptomatic treatment in order to feel better and get along better while he has the disease. This can best be done by his learning the aims of treatment so that he can vary it to meet his varying needs. It is explained that no two patients are exactly alike in their response to treatment and that the same patient must vary his treatment from time to time to meet the usual waxing and waning in intensity of symptoms or the frank remissions and exacerbations which may occur. He cannot expect good results from a prescription for neostigmine bromide tablets labeled "one every three hours" or "one three times daily after meals."

The aim of treatment is to make the patient strongest at the time when he most needs his strength, to sustain it as evenly as possible throughout the day and to avoid as far as possible the unpleasant side effects occasioned by too much medicine. In other words, he must learn from experience, by trial and error, to steer that happy course between insufficient medicine with insufficient muscle strength on one hand and too much medicine with distressing symptoms on the other. His physician, by knowledge learned from experience with other patients, can chart the course roughly but the patient must master the intricacies of his particular problem. The time required for acquiring this understanding varies. Most patients need daily guidance for approximately one week. Others, unfortunately, never become independent of precise regulation of dosage by the physician.

THE CASE OF AVERAGE SEVERITY

For the sake of clarity, let us first take up the problem of treatment in the average case. Later, we can discuss methods of managing the more severe or less severe cases and the specific symptoms requiring specific measures of treatment.

Administration of Neostigmine.—First of all, my colleagues and I prefer to examine the patient at a time when he is weakest and has had no medicine, charting carefully the results of tests of muscle strength. Then we usually administer 2 c.c. of 1:2,000 solution of neostigmine methylsulfate subcutaneously and repeat the tests of muscle strength after thirty to forty-five minutes have elapsed, a time

at which the effect of the neostigmine is maximal. This gives us and the patient a rough idea of the amount of improvement that can be expected from treatment with neostigmine. In the average case the response is considerable and the patient is much pleased with the improvement. It is explained to him that approximately the same degree of strengthening can be obtained by taking orally the tablets of neostigmine bromide and that the improvement can be maintained by repeating them as often as is found to be necessary.

The patient is given a prescription for tablets of neostigmine bromide each containing 15 mg. The container for the tablets is labeled, "Neostigmine bromide tablets, 15 mg" so that the patient becomes acquainted with the medicine used. He is instructed in the use

TABLE 1
TENTATIVE PROGRAM OF TREATMENT OF MYASTHENIA GRAVIS

Date	Time	Meals	Neostigmine Bromide Tablets (15 mg)	Reactions
1-12-47	7 a.m.		1	
	7 30	Breakfast		
	9.30		1	
	11 30		1	
	12 m.	Lunch		
	3 p.m.		1	
	5.30		1	
	6	Supper		
	7.30		1	

of a mimeographed sheet provided for convenience in recording the data important in determining his basic requirements of neostigmine. A tentative program is outlined and thereafter the patient records the time the medicines are taken, the time his meals are eaten and any reactions that occur. A sample of a tentative program of treatment is shown in table 1.

Importance of Time Relationship between Meals and Dose of Neostigmine Taken Orally—Perhaps a word of explanation is in order regarding the importance of the time relationships between meals and medication. My colleagues and I have found that difficulty in chewing and swallowing is a chief symptom of 44 per cent of our patients and is present to a lesser degree in an additional 27 per cent. Since

so many patients who have myasthenia gravis experience difficulty in chewing and swallowing, it is important that the neostigmine be taken sufficiently far in advance of meals that these symptoms will be minimal at the time the patients eat. They should eat when they are at their best. The average patient finds that neostigmine taken on an empty stomach begins "to take hold" in about twenty to thirty minutes. One more severely affected may not notice the full beneficial effect of neostigmine until forty-five to sixty minutes after the medicine is taken. In any event we have found that it is well to start with the neostigmine tablets about thirty minutes before meals. If experience shows that more time is required for maximal benefit to occur, the time of administration can be changed to forty-five or sixty minutes before meals.

It may be surprising to learn that even in the group of patients who have no difficulty in eating (29 per cent) approximately the same program is followed. Many patients experienced in the treatment of myasthenia gravis have observed that neostigmine bromide taken immediately preceding, during or soon after a heavy meal is relatively ineffective. Some patients have expressed it in this way "To take prostigmine on a full stomach is like throwing it away." If this observation is correct, and I am convinced that it is, the neostigmine taken thirty to sixty minutes before meals is of advantage in that it is more effective at that time than nearer mealtimes. Furthermore, except in the most seriously afflicted, the next succeeding dose will be taken an hour or two after meals when it is more effective than if taken sooner after the meal.

Determining the Basic Requirement of Neostigmine—Let us return to the problem of the average case of myasthenia gravis. The patient has been given a tentative program of treatment with one tablet of neostigmine bromide (15 mg.) thirty minutes before meals, midway between meals and in the early part of the evening. The physician may find at the next visit that the patient did well during the morning hours but during the late afternoon he was less strong and had difficulty in eating his evening meal. The patient next tries taking two tablets of neostigmine bromide at 3 and 5:30 p.m. instead of one tablet and finds that his condition is much better when he takes the larger doses. Another patient may find that he does not need any medication during the morning and can get along well on four tablets daily starting at 11:30 a.m. My colleagues and I have found that 64 per cent of our patients, the group considered to have the disease in average degree of severity, require three to nine tablets of neostigmine bromide daily.

Adjuncts to Treatment with Neostigmine: Ephedrine, Guanidine and Potassium.—When the average patient has acquired an understanding of the aim of treatment with neostigmine we allow him to re-

turn to as nearly normal routine as possible. Of course if his job is a strenuous one, such as heavy farm labor, it may be obvious in advance that he must drastically curtail his work or change his occupation.

After the patient has found by trial and error his average requirements of neostigmine we have him test the effects of adding ephedrine sulfate to his routine of treatment, discontinuing it after one week. If, by comparison of his condition while taking ephedrine with that while taking neostigmine only, he can demonstrate additional benefit from the ephedrine, he continues to take it indefinitely. We have found that 39 per cent of our patients continue the combination of neostigmine and ephedrine. We usually prescribe the ephedrine sulfate in capsules containing $\frac{3}{8}$ grain (24 mg) and the patient usually takes them in the morning, at noon and not later than 4 p.m., since there is a tendency for ephedrine to cause insomnia if taken later. Some patients may omit the afternoon dose. Some find the ephedrine to produce an unpleasant sense of restlessness and they may discontinue it altogether or reduce the dose to $\frac{1}{8}$ grain (8 mg) two or three times daily. Of course, if the patient is elderly, ephedrine must be used cautiously because of its tendency to interfere with micturition.

Formerly, my colleagues and I insisted that our patients undertake similar trials using guanidine hydrochloride with the basic neostigmine regimen and that during other periods they try the effects of potassium chloride. However, since so few continued either adjunct for long, we seldom urge them to do so now.

Unpleasant Reactions to Neostigmine and Measures to Prevent Them.—Since the great majority of patients experience some unpleasant reactions from neostigmine, perhaps it is best to discuss these reactions and the measures to prevent them while considering the treatment of myasthenia gravis of average severity.

The commonest unpleasant symptoms resulting from neostigmine are gastro-intestinal in origin and range in severity from neostigmine sense of a lump in the epigastrium and mild abdominal cramps to severe abdominal cramping, diarrhea, nausea and vomiting. Although these symptoms also occur when the drug is administered parenterally they are perhaps more likely to result from neostigmine bromide taken orally.

In more severe reactions and usually superimposed on the gastro-intestinal symptoms enumerated in the preceding paragraph, faintness and even syncope occur.

Increased salivation and perspiration occur regularly and are seldom troublesome.

Muscle twitching (fasciculation) is particularly prone to occur among nonmyasthenic patients taking neostigmine and seldom occurs to a distressing degree among patients who have myasthenia gravis.

The prevalence of gastro-intestinal symptoms, particularly early in

the course of treatment, is the chief deterrent to the taking of an amount of neostigmine sufficient to bring about the best response as far as the weakened muscles are concerned. Although atropine and other antispasmodics are helpful in preventing distress they too often fail to control the symptoms entirely. The administration of $\frac{1}{150}$ to $\frac{1}{100}$ grain (0.43 to 0.65 mg) is often used but my colleagues and I prefer tincture of belladonna since by virtue of its being in liquid form the optimal dose is more easily determined. We have found 10 to 20 drops (0.6 to 1.2 cc) of tincture of belladonna taken fifteen minutes before each pre-meal dose of neostigmine to be fairly effective. If its administration fails to achieve the desired result other measures are sometimes effective. Since the patient is most likely to suffer distress when the neostigmine is taken on an empty stomach, particularly from the first dose in the morning, we have found that taking a little food, such as a cracker or two or a small glass of milk, at these times may be helpful. One patient carried a thermos bottle of milk and drank about 4 fluid ounces (118 c.c.) each time she took neostigmine. Others have found relief by beginning the meal sooner, within fifteen to twenty minutes, instead of thirty to forty-five minutes, after the pre-meal dose. Unfortunately, too often all of these measures fail to eliminate the gastro-intestinal effects and the patient chooses to take substantially less neostigmine than that producing the maximal strengthening effect on the muscles.

THE EXCEPTIONAL CASE

Cases of myasthenia gravis may be exceptional in many ways but at this point in the discussion I refer to those that from the standpoint of treatment are exceptionally mild or severe or in which there are specific disabilities demanding specific treatment.

The Exceptionally Mild Case.—Patients who experience exceptionally mild symptoms of myasthenia gravis are easily cared for. They may need no treatment other than the advice to avoid exceptionally strenuous activities. Table 2 shows the medicines required in 100 consecutive cases. Four patients needed no medication and one required only ephedrine.

The Exceptionally Severe Case.—Our greatest interest must be in those cases which are exceptional because of the severity of the myasthenia. The severity of the muscle weakness alone is not always the most important prognostic index. The distribution of the weakness is often more important. For instance, a patient may have so much weakness of the muscles supplied by the oculomotor nerves that he cannot move his eyes in any direction. As long as the myasthenia gravis remains limited largely to these muscles his disability is not great. However, another patient with less severe weakness of the muscles supplied by the other cranial nerves may have great difficulty in eating.

TABLE 2
MEDICINE REQUIRED DAILY BY 100 CONSECUTIVE PATIENTS
WHO HAD MYASTHENIA GRAVIS

Dosage	Patients
Neostigmine Bromide	
None	5
1 or 2 tablets (15 or 30 mg)	4
3 or 4 tablets (45 or 60 mg)	20
5 or 6 tablets (75 or 90 mg)	23
7- 9 tablets (105-135 mg)	21
10-19 tablets (150-285 mg)	20
20-30 tablets (300-450 mg)	4
More than 30* tablets (more than 450 mg)	3
Total	100
Ephedrine Sulfate	
None	61
1- 3 doses ($\frac{1}{2}$ grain [24 mg] each)	38
7 doses ($\frac{1}{2}$ grain [48 mg] each)	1
Total	100
Guanidine Hydrochloride	
None	90
8-10 tablets (125 mg each)	9
19 tablets	1
Total	100
Potassium Chloride	
None	93
20-35 gm.	2
Total	100

* Highest requirements 70 tablets (1,050 mg) of neostigmine bromide plus 7.5 gm. of neostigmine methylsulfate parenterally

and be threatened constantly with choking or aspiration pneumonia. Weakness of the muscles of the extremities, although severe, in itself is no particular threat to vital processes, whereas a similar degree of weakness of the muscles of respiration would be especially ominous.

Myasthenia gravis of steadily increasing severity causes the physician more concern than does that of severer degree that has remained stationary over a long period.

Thus, many factors must be taken into consideration in determining the prognosis of myasthenia gravis. The over-all course of the disease, the distribution of the affected muscles and the degree to which the muscles are involved are important. Perhaps one of the most important single prognostic indexes, however, is the patient's response to neostigmine. Two patients without medication may have equal difficulty in swallowing, breathing or moving their extremities. One of them may respond so well to neostigmine that a few tablets daily enable him to lead a relatively normal existence. The other may remain bed-fast even though taking large doses of neostigmine. Some authors refer to the relative ineffectiveness of neostigmine as indicating that the patient has become "neostigmine-fast." I prefer, as does Viets, to look on this condition as meaning that the myasthenia gravis has become so severe that neostigmine is no longer effective. These same patients may undergo a remission and the neostigmine again becomes as beneficial as it is in the average case, although it was taken continuously. The term "neostigmine-fast" seems to imply that the patient acquires a tolerance to the drug, without any significant change in the severity of the disease itself. It seems to me that it is more logical to think of the disease as becoming so severe that neostigmine is no longer significantly effective.

More specifically, let us return to management of the patient who is exceptional because of the severity of his myasthenia. Table 2 shows that 27 per cent of the patients required ten or more tablets of neostigmine daily. Furthermore, not all of the 73 per cent who took less than ten tablets a day got along well on this amount of neostigmine. Nine of the group of seventy-three found it necessary to restrict their activities seriously. Some of these were in the group in which there developed severe gastro-intestinal symptoms from neostigmine which prevented them from taking sufficient medication to lead a more normal existence.

Although the average patient finds that one or two tablets (15 or 30 mg.) of neostigmine per dose is required for maximal benefit the more severely afflicted may require three or four tablets (45 or 60 mg.) per dose. Furthermore, the strengthening effect is usually slower in becoming manifest and is maintained over a shorter period than with the average patient. Therefore, it may be necessary to repeat the doses more frequently. While the average patient seldom requires

bulky proportions, which has run a benign course (many months or years) The location is usually intrathoracic or retroperitoneal

TREATMENT is by surgical removal

Chromaffinoma.—This is a unique tumor of sympathetic nerve origin and is recognized by the presence of a mass of moderate size in the flank or abdomen It may produce hypertension, frequently paroxysmal in type

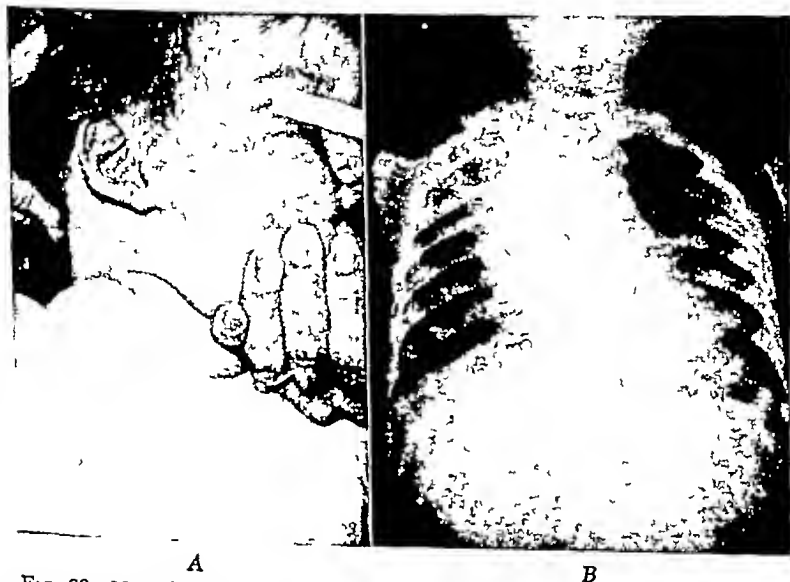


Fig 60—Neuroblastoma (S M, female, aged 14 months) Following radium therapy given elsewhere to a hemangioma, in the right supraclavicular fossa, a mass was noted (A) in this region An aspiration biopsy at Memorial Hospital was reported as neuroblastoma, probably metastatic in this position X-ray of thorax (B) shows an upper mediastinal mass, right side, erosion of the 3rd and 4th ribs and enlargement of the interspaces in this region. (The patient showed no evidence of disease on December 6, 1946, sixteen months following the institution of x-ray therapy to mediastinum)

TREATMENT is by surgical excision It should be realized, however, that removal of this tumor, which is responsible for the hypertension, may suddenly deprive the circulation of vascular supportive substances that this neoplasm produces, resulting in irreversible shock

TUMORS OF THE EYE AND ORBIT

The two most common varieties of tumor of the eye and orbit are orbital sarcoma and retinoblastoma (*glioma retini*)

Orbital Sarcoma.—This neoplasm appears as a swelling about the orbit, usually involving the entire orbital fossa At times it may extend

neostigmine during the night those who are more ill often do. It may be necessary for the patient to be awakened one or more times during the night in order to prevent crises occasioned by severe respiratory embarrassment, inability to swallow or talk or reach his medicines on a table at the bedside

Maximal Dose of Neostigmine.—The question is frequently asked by patients and physicians, "How much neostigmine can be taken safely?" Usually it is sufficient to reply that, in order to be able to remain at his office, one of our patients took, over a period of several weeks, seventy tablets of neostigmine bromide (1,050 mg) plus five injections of the diagnostic ampule of neostigmine (each containing 15 mg of neostigmine methylsulfate and $\frac{1}{100}$ grain [0.65 mg.] of atropine sulfate) every twenty-four hours. Naturally, I do not look with favor on such a program. Anyone who is seriously weakened should remain in bed and thereby be able to get along with less neostigmine.

The amount of neostigmine that can be taken safely is variable. It has been reported¹⁰ that one normal subject was considered seriously ill after taking three tablets (45 mg) of neostigmine bromide. Furthermore, the taking of excessive amounts of neostigmine can in itself lead to paralysis, at least among persons without myasthenia.

In fact, Harvey, Lilienthal and Talbot have utilized the paralyzant effect on patients of 0.5 to 0.1 mg of neostigmine methylsulfate injected into the brachial artery and confined to the forearm and hand by an inflated cuff around the arm as a test to exclude myasthenia gravis. The muscles of the forearm of the patient who has myasthenia gravis are strengthened by performance of the same test, thus demonstrating that the myasthenic patient can tolerate, or actually benefit from, concentrations of neostigmine which weaken the muscles of the subject who does not have myasthenia gravis.

Thus, theoretically at least, it may be possible to give the patient with myasthenia gravis too much neostigmine. I would agree with Viets, however, that in crises this is an error which is less likely to be made than the error of not giving enough neostigmine. Viets has given neostigmine methylsulfate intravenously to the advantage of patients in crises. He has recommended up to 30 mg per hour. Dr. C. F. Code and I have studied the effects of neostigmine methylsulfate in a mixture of beeswax and peanut oil. We have found that 10 mg or more may be placed subcutaneously and the desired effect from the neostigmine may be prolonged to from ten to approximately seventy-two hours. The problem of maximal dosage of neostigmine will be discussed further under subsequent topics.

Specific Disabilities.—*Diplopia and Ptosis*.—My colleagues and I have found that the earliest symptom of 56 per cent of our patients has been ptosis, diplopia or both and that 94 per cent of our patients

had had these symptoms by the time of their first examination at the Clinic. In 10 per cent of the patients diplopia or ptosis or both were the only symptoms and in 55 per cent they were important symptoms.

Ptosis is less frequently troublesome to the patient than diplopia and is usually controlled satisfactorily by neostigmine. We have never found it necessary to advise one of the various operations for the correction of ptosis in myasthenia gravis but three of our patients in a group of 230 cases gave the history that this operation had been performed before the diagnosis of myasthenia gravis had been established.

Diplopia is frequently transient and slight and responds well to small doses of neostigmine. Occasionally the paralysis of the oculomotor muscles is so complete that the eyeballs are fixed in normal position and diplopia is not complained of. In such cases the administration of neostigmine may actually produce diplopia by its unequal strengthening effect on the extra-ocular muscles.

Frequently it is found that average doses of neostigmine improve the strength of the extra-ocular muscles, yet do not do so perfectly and diplopia is unrelieved. In such cases it is our policy to prescribe a relatively small amount of neostigmine, just enough to control ptosis and other symptoms, and advise that the vision of the poorer eye be blurred by an appropriate device. Some prefer a frosted lens or one of crackled glass. My colleagues and I have found that the application of clear fingernail polish, which is stippled with a brush as it dries, to the inner surface of the lens as suggested by Mattis is highly satisfactory. The polish can be removed easily with commercial polish remover and the other lens treated in the same way if it is believed that both eyes should be used alternately. In other words, in cases in which diplopia is not readily controlled with neostigmine no effort is made to eliminate this condition with large doses of neostigmine which are not needed for strengthening muscles more vital to the patient's general welfare.

Dysphagia—Dysphagia is an important symptom in approximately 10 per cent of our cases. As far as possible this symptom is combated by administering the proper amount of neostigmine bromide at the optimal time before meals. Often one or two tablets of the bromide (15 to 30 mg.) thirty minutes before meals is effective. Sometimes three or four tablets (45 to 60 mg.) must be given forty-five to sixty minutes before meals. In many cases, however, the unwanted gastrointestinal symptoms prevent the taking of adequate amounts of neostigmine bromide. Then we may find that the patient does better on four to six smaller meals daily. Occasionally we find that 0.5 to 1.5 mg. of neostigmine methylsulfate administered subcutaneously twenty to thirty minutes before meals solves the problem of maintaining adequate nutrition. The myasthenic patient should not be allowed

to become debilitated through lack of adequate nutrition. If simpler measures, such as the adjustment of the dosage of neostigmine, described earlier in this paragraph, and the feeding of soft and ground foods, do not suffice, feedings by stomach tube should be initiated. In serious cases we find it advisable to teach the patient or some member of the family to insert the stomach tube and prepare a suitable formula for administration by tube.

The formula shown in table 3 has been found satisfactory for feeding by tube in myasthenia gravis. This formula makes approximately 1,500 cc and contains 2,550 calories, 212 gm of carbohydrate, 108 gm of protein and 143 gm of fat. It is adequate in minerals and vitamins except for niacin (9 mg). The ingredients are mixed with a Dover egg beater or an electric mixer. The formula is kept in a re-

TABLE 3
FORMULA FOR FEEDING, BY STOMACH TUBE, PATIENTS
WHO HAVE MYASTHENIA GRAVIS

Ingredients	Weight, gm	Approximate Measure
Evaporated milk	1,000	1 quart
Cream (20 per cent)	200	1 glass
Orange juice	200	1 glass
Corn syrup	100	$\frac{1}{2}$ cup
Eggs		4
Yeast powder	20	2 tablespoonfuls

frigerator. After stirring, the amount required for each feeding is removed and warmed to body temperature over hot water.

In certain cases of crisis a nasal tube has been left in place for several weeks, through which food, water and medicines were administered.

In general my colleagues and I urge our patients to partake of a well-balanced diet containing adequate calories and vitamins. Vitamin supplements are not prescribed unless there is reason to believe that the diet has been inadequate. Dr. Harriet Edgeworth, herself a myasthenic patient, believes that excessive carbohydrates have a weakening effect and consequently her advice regarding the avoidance of excessive carbohydrate intake is passed along to the patient. Patients' statements regarding the effect of alcohol on their symptoms have been conflicting and we have not attempted any objective measure of its influence.

Respiratory Failure—Respiratory failure is the actual cause of death in most cases of myasthenia gravis. Usually there is adequate warning that respiration is failing but too often the warning is misinterpreted as a manifestation of anxiety. The patient becomes restless, complains of difficulty in breathing and may state that he fears he is about to die. Casual examination may not show any significant change in the patient's condition. Usually he is not cyanotic and thoracic excursion may appear to be as adequate as when he is not concerned. Baker and Brown observed these same manifestations among certain patients who had bulbar poliomyelitis and were able to correlate the symptoms with a decided fall in the degree of oxygen saturation of the blood. If the patient who has these symptoms is not treated appropriately he may suddenly stop breathing, lose consciousness and soon die. Of course, patients seriously ill with myasthenia gravis tend to be apprehensive and it is not always easy to determine the motivating factors. However, experience has shown that such symptoms cannot be dismissed lightly. It is wise to make certain that actual respiratory failure is not producing them.

In such cases it is well to study the time relationships between the onset of the apprehension and the administration of neostigmine. If the apprehension appears forty-five minutes or more after a substantial dose of neostigmine has been given and disappears within five to twenty minutes after administration of another adequate dose one can be relatively certain that the apprehension is a direct result of respiratory insufficiency.

Periodic attacks of dyspnea are another ominous sign in myasthenia gravis. Rarely, crowing respirations occur and in one of our cases paresis of the abductors of the vocal cords was observed to account for it. It is possible that tracheotomy may be necessary at times as a lifesaving procedure. In the case referred to, the symptom was alleviated by more rest and more frequent administration of neostigmine.

I cannot overemphasize the value of artificial respiration (preferably in a Drinker type of respirator), mechanical aspiration of secretions in the pharynx and bronchoscopic aspiration of tracheobronchial secretions in the management of respiratory crisis. Clagett and I^{5, 6} are convinced that several patients experiencing such crises after thymectomy would not have survived had these measures not been used. Early in our work we used the Drinker type of respirator after the crisis was well developed. Now we use it if we believe a crisis is impending. We find that an apprehensive patient may be literally wearing himself out in his efforts to breathe and to rid himself of secretions in the respiratory tract and through the purposeless movements symptomatic of his discomfort. In such cases an increase of the dose of neostigmine may lead to an increased production of thick saliva. Thus the patient fails to obtain relief with greater dosage. Almost at once

after being placed in the respirator his condition may improve. If not, it is well to perform bronchoscopy and remove whatever obstructive secretions are found in the trachea and bronchi. Often inspissated mucus is found. In such cases adequate humidification helps prevent the inspissation of the mucus. While the respirator is in use oxygen can be administered if it gives additional relief. Sedatives and morphine can be more safely administered to insure rest. Of course, penicillin is given to prevent or combat pneumonia and the patient's position in the respirator is shifted periodically to overcome hypostasis.

When a patient is subject to crises of choking, respiratory failure or inability to talk, he or some member of his family is instructed in the hypodermic administration of neostigmine methylsulfate. My colleagues and I have some of our patients carry with them a sterile hypodermic syringe, ampules of neostigmine methylsulfate and a card reading, "I have myasthenia gravis. In case of emergency inject two ampules of prostigmine into the muscles of my thigh. Then call a doctor."

HYPERTHYROIDISM ASSOCIATED WITH MYASTHENIA GRAVIS

In our experience at the Clinic approximately 6 per cent of patients with myasthenia gravis either have associated hyperthyroidism or have had this disease before the onset of the myasthenia gravis. It seems to us that the frequency with which the two diseases are associated is too great to be dismissed as due to coincidence. Furthermore, we have come to look on the combination, particularly if either or both diseases are severe, as a particularly unhappy one. At least, our results from subtotal thyroidectomy and treatment with thiouracil have not on the whole been favorable. And yet there are exceptions. In the case reported by Kowallis, Haines and Pemberton there has been a complete remission of both diseases for a period of more than five years after subtotal thyroidectomy. In another most interesting recent case it seems likely that the excessive administration of thyroid resulted in true myasthenia gravis, which responded to neostigmine. The symptoms of myasthenia gravis subsided entirely on withdrawal of thyroid. These two cases leave us with the impression that the hyperthyroidism may at times be primary. For that reason, it seems wise to treat the hyperthyroidism in anticipation of improving the myasthenia gravis. The choice of treatment must necessarily be dictated by the condition of the patient.

The basal metabolic rate of many myasthenic patients is low. Except for one patient who had postoperative myxedema, my colleagues and I cannot remember any patient whose condition was benefited by the administration of thyroid. Conversely, it seemed definite that administration of thyroid increased the weakness of some patients. Spe-

cifically, in one of our cases the metabolic rate, which had been low, progressively approached normal when administration of thyroid was discontinued and treatment with neostigmine was instituted

THYMECTOMY

Stimulated by the reports of Blalock, Mason, Morgan and Ruven in 1939 and of Campbell, Fradkin and Lipetz in 1941, Clagett, Good, McDonald and I undertook an intensive study of the value of thymectomy in myasthenia gravis. Good soon found that by use of roentgenoscopy and roentgenograms of the thorax made in lateral and sometimes oblique positions as well as in the ordinary postero-anterior position he could demonstrate thymic tumors in more than 15 per cent of our cases of myasthenia gravis.

Surgical exploration and necropsy have demonstrated that the roentgenologic techniques developed by Good are surprisingly accurate and we believe that this incidence of 15 per cent approaches the actual incidence of thymic tumor among patients who have myasthenia gravis.

Although at the present time fifty-six of our patients have undergone operation for removal of the thymus or thymic tumors, we have analyzed the results in only the first thirty-two cases.^{5, 6} From this study we find that approximately 60 per cent of the patients have shown unequivocal improvement varying from moderate degree to complete remission. At first glance this percentage of improvement would appear most encouraging. However, in view of the fact that remissions are prone to occur in myasthenia gravis, that the course cannot be predicted with sufficient certainty to say that remissions would not have taken place spontaneously and that thirty-two cases are too few for reliable statistics, we believe it is best to withhold final judgment. It is probable that when 100 patients who have undergone thymectomy have been studied for at least one year after operation and the results compared with those for a group of controls a reliable opinion will be obtained. Meanwhile, after a frank discussion of these facts with the patient we offer thymectomy as a possible means of influencing beneficially the fundamental course of his disease.

ROENTGEN IRRADIATION OF THE THYMUS

The value of roentgen irradiation of the thymus is even more difficult to determine than the value of thymectomy. The study of certain specific records of cases in our series in which remissions have regularly followed roentgen therapy makes it difficult to dismiss roentgen irradiation as valueless. Yet in a study of 100 consecutive patients treated by roentgen irradiation of the thymus only 18 per cent seemed to experience a remission during the ensuing twelve months. How-

ever, in retrospect we are almost certain that the amount of roentgen therapy administered was grossly insufficient. Dr McDonald had the opportunity of studying histologically thymuses and thymic tumors removed at varying intervals after similar amounts of roentgen therapy had been given and has been unable to detect any changes which could be attributed to the irradiations.

For the time being we believe it advisable to reserve final judgment as to the value of roentgen irradiation of the thymus. If in time surgical extirpation of the thymus is proved to be of undoubted value it may be possible to devise technics or roentgen therapy which are equally effective. At the present time, if we decide that the patient is too ill to withstand surgical treatment we often advise roentgen therapy. The technic used at the present time by Dr Leddy, our colleague in the Section on Roentgen Therapy, is irradiation of the thymic area through two anterior and two posterior fields cross-firing the anterior mediastinum from the level of the cricoid cartilage to the diaphragm. The technical factors usually are in the neighborhood of 130 kv, 6 ma, 5 mm aluminum filter, distance 40 cm, time, eight to fifteen minutes per field, a dose of 32 r per minute. When a mediastinal tumor is present, the time averages sixteen minutes per field. The treatments are given on successive days and the series is repeated in one to two months.

DRUGS TO BE AVOIDED IN MYASTHENIA GRAVIS

I have already stated that there is clinical evidence that thyroid, except in myxedema, is not of value and may actually affect the myasthenic patient adversely. There is no doubt that two drugs, quinine and curare,⁸ greatly exaggerate the symptoms of myasthenia gravis. Their effect is so great that they serve well as clinical tests for this disease.^{2, 7, 11} Not only should they not be prescribed in myasthenia gravis but it behooves the physician about to administer these drugs to any patient to consider whether or not the patient could possibly have myasthenia gravis. Atabrine in therapeutic doses shows no appreciable effect on the weakness of the myasthenic patient and should be used instead of quinine in the treatment of malaria if the patient is myasthenic.

There may be other medicines which affect myasthenia gravis deleteriously and consequently it is wise to use new and untried medicines cautiously.

CONCLUSIONS

The thought cannot escape me, as I find that this discussion of treatment of myasthenia gravis, limited as it is to the practical aspects, turns out to be rather lengthy, that the length in itself reflects the fact that the final answer to the treatment of myasthenia gravis eludes us still. The space devoted to treatment in an article on pernicious

anemia before the advent of liver extract was relatively large in comparison to the space required now to deal with what is really effective treatment I trust that the rapid advances being made in knowledge of the physiology of nerve and muscle may soon result in a simple method of promptly curing myasthenia gravis In the meantime, may the suggestions in this paper contribute to making the lot of the patient who has myasthenia gravis easier!

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SYMPTOMATIC TREATMENT IN HYSTERIA

PHILIP H. HEERSEMA

TREATMENT of the psychoneuroses and particularly the hysterias has undergone considerable change during the past ten to twenty years. This has been due largely to the more intensive study of the psychopathology, that is, the mechanisms involved in symptom formation. As a consequence, emphasis has been placed on the causal approach in therapeutic management, and this has served, in a measure, to supplant the older methods which tended to treat by attacking the symptoms directly. In other words, suggestion, persuasion, hypnosis and various forms of direct suggestion have fallen more or less into a state of disrepute. Such methods, however, by no means have lost their importance, and the volume of patients who present symptoms of hysteria or other psychoneurotic symptoms warrants at least a review of these less profound, but many times adequately effective, methods. I speak, principally, of the use of simple direct suggestion in the symptomatic treatment of some of the psychoneuroses, notably, the conversion hysterias.

GENERAL CONSIDERATIONS

We know that direct suggestion has been responsible for dramatic "cures" throughout the history of medicine as well as in the pseudo-healing arts. We are indebted to Sigmund Freud—one of the pupils of that master of suggestion, Chareot—for his critical examination of suggestion as a therapeutic technic and for many of our clearest concepts of the pathogenesis of the neuroses. But, in a certain sense, the confirmatory evidence of many of Freud's original hypotheses, with their outstanding contributions to the understanding and treatment of mental disease, also has served to crowd the simpler, superficial symptomatic type of treatment into a relative state of impotence, so that the use of such treatment is admitted to one's colleagues only with apology.

One may deplore the little attention and space that are given in the literature to techniques of treatment of the neuroses aside from the psychoanalytic techniques. Probably much of this deficiency is due to an unwillingness on the part of physicians to advocate superficial types of therapy in the face of the elaborate discussions of deeper causal therapy, exemplified by the psychoanalytic approach. I am confident that the vast majority of psychiatrists are grateful for the understanding of psychopathology and mental mechanisms which psychoanalysis has afforded. Yet no one is more acutely aware than the analyst of the

self of the limitations in the treatment of certain patients. Moreover, I am sure that the analyst himself would subscribe to the less intensive treatment of the acute or subacute hysterical symptoms in view of the fact that there is a large group of patients whose age and intelligence, as well as difficulties relating to time and distance, preclude the possibility of intensive therapy.

It has been pointed out repeatedly that the hysteric escapes into illness as the solution of some personality problem or some conflict in which the instinctual drives come into direct conflict with the rules and demands of his social self. The "secondary gain" derived from this adjustment is frequently mentioned in connection with the hysteric, since the hysterical patient best demonstrates the conversion of psychologic conflict into physical symptoms with benefits to himself through acceptable avoidance of duty and yet satisfying the conscience at the same time. As a matter of fact, many psychiatrists demand that some rather obvious secondary gain to the patient be present, before they are willing to make a diagnosis of hysteria. However, it is not necessary that this so-called gain be obvious, and indeed often it is only on searching investigation that the physician is able to recognize the benefits which the hysterical reaction has afforded the patient. It is well to remember that all psychopathologic reactions are in the nature of an adjustment, ostensibly effected for the benefit of the individual concerned.

It is also important to remember that the behavior manifestations of psychoneurotic and psychotic disturbances have *meaning* to the patient. The psychoneuroses, with their close contact with reality, should be considered disturbances of social behavior which act as the medium of reconciliation between the inner striving or drive of the individual and the demands of society. Analysis of these problems is more clearly seen in hysteria, with its dramatic and frequent symbolic manifestations, than in any of the other psychoneuroses. The hysterical reaction frequently is called a "primitive mode of expression" and a relatively direct symbolic expression of the conflict. Symbolic expression of these drives may employ a certain member or organ which has been critically involved in the external situation which reactivated the unconscious. This may be evident in hysterical blindness, when the individual has witnessed something which reactivated a painful visual image in the unconscious and something which he considers too painful to witness again. We find this choice of symptom formation in the case of paralysis of those extremities which have been raised in anger against members of the family. However, the onset of symptoms of hysteria need not always be as acute or as dramatic as this.

In every case, nonetheless, we are forced to deal with emotions or affects which accompany the proposed but unacceptable behavior.

posteriorly and produce symptoms of pressure on the globe (proptosis). The growth may occur at any age and not infrequently affects infants.

TREATMENT is by surgical removal with enucleation of the globe. Irradiation may occasionally be employed postoperatively, when indicated.

Retinoblastoma—This is one of the well known varieties of children's cancer. It is a tumor of very early life and is embryonal in nature. Although present at birth, it may not become evident until weeks or months later. Most of our forty-eight cases were noted before $5\frac{1}{2}$ years of age, the average being 14 months. The neoplasm is bilateral in many instances (more than 50 per cent in our series).

The disease may be suspected from the following symptoms and physical findings: orbital bulge, strabismus, and a pupil which has a gray, white, yellow, green or glassy reflex. Very rarely the reflex is red and the pupil may be dilated.

The symptoms referable to vision are frequent stumbling and turning the head so that the unaffected (or less affected) eye may be used for vision. One mother observed that when she covered her baby's good eye, the baby cried, apparently in fear. This was obviously due to the complete darkness in which the child found himself when deprived of the use of his only functioning eye.

Ophthalmoscopic examination will usually reveal a large pinkish-white tumor, sometimes containing calcareous deposits, and a few blood vessels visible on the surface of the tumor. Detachment of the retina may also occur.

Retinoblastoma must be differentiated from (a) simple retinal detachment, which usually vibrates more following motion of the orbit than retinoblastoma, and (b) congenital anomalies, such as persistent tunica vasculosa lentis (retrolental fibroplasia) which may be accompanied by other congenital defects and inflammatory processes including pseudoglioma. A suggestive history of infection is not usually found with retinoblastoma and the inflammatory lesion, moreover, is frequently yellow and presents a smooth appearance. Confluent tubercle and histoplasmosis may be differentiated by the presence of an associated systemic disorder. Finally, retinoblastoma must be differentiated from retinitis, a very uncommon disorder in young children.

TREATMENT is by enucleation of the affected eye in unilateral cases and in bilateral cases the more involved eye should be enucleated. The remaining eye may be treated by fractionated irradiation, described by Martin and Reese,¹ a method of treatment which has given encouraging results in some instances.

The eventuality of loss of vision even following irradiation must be considered. The advantage offered by irradiation is the possibility of saving the vision of the remaining eye, but it must be recognized

The instinctual drives may frequently or even constantly rebel, but if man would continue as a respectable member of society, it becomes necessary for him to put down these rebellions. Consequently, methods such as energetic pursuit of hobbies, different types of work or avocations—that is to say, substitution or sublimatory modification—have served to dissipate the pain of these frustrations or thwarted strivings of the instincts. In the individual in whom the drive may be too intense, or in the individual who is less well organized (lessened stability in his reactions and endowed with less ability to exercise judgment), a psychoneurotic reaction may result.

PSYCHOPATHOLOGIC CONSIDERATIONS

It is important to pay attention to the Freudian concept of the "unconscious" and in particular to the mechanism of repression. The "unconscious" serves as a repository for the vast majority of our memories or mental images which are not necessary to the conscious functioning of the social individual. The vast majority of these mental images and memories are neutral, that is to say, they do not have any critical associated feeling tone of either pleasure or pain. There are, however, a number of past experiences in which, for some particular reason, the mental image remains in the unconscious and the painful affects—that is, the emotional tone or the feeling associated with that mental image—have been split off to float around in the individual's consciousness in terms of malaise, or indescribable sense of ill-being, tension, nervousness and the like. The mental image may be considered as repressed when it has been totally forgotten, whereas the attendant emotion is irrepressible.

The "unconscious" serves as a storehouse for one particularly important group of painful memories, namely, those experiences of the early exploring adjustment period. We must remember that the child is not a socialized being at birth, but that he is an instinctive creature endowed with certain abilities, energies and drives by which he is able to gratify these instincts. Gratification consequently is pleasurable, such as his early demands for food being satisfied by suckling. As the child becomes more socially conscious, many of the forms of gratification, with which pleasure was an associated aspect, gradually become impressed on the child as being unworthy or forbidden. The result is the repression of the mental images in one's childhood and the relegation to the unconscious of the majority of childhood experiences occurring before this socialization age of four or five, when his social adjustment is increasingly important. Repression acts entirely without our knowledge, but is, nevertheless, a powerful force. Dane likened repression "to the pressure of the atmosphere, which although unseen and unnoticed directly, yet is responsible for many of the facts observed in Nature. . . . Repression manifests its greatest activity during

the first five years of his life when he has to give up so much and bend his mental apparatus to the pressure of his cultural surroundings" It is probable that the unconscious contains more than simply repressed material, but we are not concerned with this, for the repressed material is the critical material, that is, the painful memory and objectionable mental images whose recall and reactivation we are anxious to avoid. To extend this picture to include the hysterical reaction, and particularly the so-called acute hysterical symptoms, we can picture a quiescent unconscious just preceding the hysterical reaction. The individual then may be confronted with a constellation of external forces which serve to activate this "unconscious" and to stir up sufficient urges which demand outlet. Direct expression of these urges is socially impossible. Therefore, some vicarious method of expression must follow.

In a situation involving an acute hysterical reaction, a prompt, and oftentimes dramatic, dissipation of the affect, or emotional force motivating the symptoms, by means of active suggestive therapy may be sufficient to allow the repressed ideational content to slumber peacefully on in the unconscious for a number of months or years. Obviously, when such a conflict situation involves interpersonal relationships of a repeated and painful nature, the conflict is represented by more than a passing hysterical symptom and may become somatized, that is, converted into a constant physical symptom. Thus, we often see vaginismus as a hysterical symptom acting as a defense measure against coitus, possibly a situation in which the idea of coitus represents relations with a father image residing in the husband, which is probably due to inadequate emotional emancipation from a natural childhood attachment.

In a situation of this latter type, simple direct suggestion, of course, probably will not be effective, and more profound therapy must be employed to correct the symptoms.

MANAGEMENT OF CONVERSION SYMPTOMS

The hysterical reaction represents the settlement of a conflict at a profit, that is to say, a settlement in the patient's favor. Thus, it is well to recognize that there are certain advantages to the hysterical reaction which afford considerable resistance to change through treatment. In short, the cure must offer more than the illness, in the coin of the personality. Let us remember, however, that in the hysterical patient we are dealing with a socially conscious individual, and that he is therefore susceptible to certain forces that may minimize the advantages of the hysterical reaction. In addition to this, the lapse of time may change the situation. A certain amount of resistance from the patient's environment, a skepticism on the part of friends who think that the patient may be "putting on," or the suggestion from

the physician that the difficulty is "all in your head," may demand that the patient repeat or fix the hysterical symptom or symptoms more deeply than the, let us say, *transitory hysterical situation* demanded. In other words, by the patient's having been committed to a hysterical-symptom solution of the problem, it may become necessary for him to defend that stand, simply because he "loses face" and his ego suffers if he does not defend it. In the treatment of the hysterical patient, the physician's ability to leave an open door, or to open a door, whereby the patient may make a *graceful exit* from his symptoms, should be considered as one of the most important features of his therapy.

It is probable that much may be accomplished in this superficial treatment by the search for conflict factors, followed by the use of desensitization and re-education approaches. However, at the onset, desensitization and re-education are not so effective with the hysterical psychoneurosis as with some of the other psychoneuroses, which may be in part because the patient who is subject to hysterical symptoms presents more histrionic elements in his make-up, and requires something more dramatic than the logical analysis of the etiologic factors to establish rapport. The method of direct, active suggestion in the symptomatic treatment of hysteria provides the opportunity for this *graceful exit* from illness, for we must remember that the hysterical patient is very definitely in touch with the real world about him. This is a world of social demands and exacting rule, and in these terms, it is not easy for the individual to admit either to himself, were he so consciously disposed, or to his curious friends, that the symptoms have disappeared simply through discussion, or by "talking to the doctor." To his layman friends this brands him as a neurotic, which still is a term of opprobrium in society. It allows a much more satisfactory solution for the patient to state that he had received some medicine, heat, electricity or other physicochemical agents in treatment, which agents have at least a modicum of reason as a basis for the treatment of symptoms. The physician should make it a rule to acquaint the individual patient with the fact that psychologic factors are operative in the formation of his illness, although the physician is perfectly aware of the fact that many patients wish to believe (and may so explain their improvement) that it required some physical means to correct their physical disturbance, whether it was photophobia or paralysis or any one of the multitude of symptoms which the hysteria may manifest.

Ideally, the use of suggestion should be considered analogous to that of a catalytic agent, inasmuch as it speeds up or initiates the end result without creating any physicochemical change. The patient always should be informed before dismissal, irrespective of how complete or how satisfactory the symptomatic cure may be, of the role that the

physiotherapy, the faradic current, the hypnosis or the medication has played. In spite of the long-exercised resistance of the hysteric, it is amazing how well an honest formulation just such as this may be received by the patient after his immediate symptomatic cure or improvement, which, of course, has already permitted the establishment of excellent rapport.

The hypothesis may be advanced here that the hysterical symptoms appear as a solution of a temporary problem created by a constellation of various external forces. In other words, the passage of time may sufficiently attenuate these forces so as to make the hysterical symptom unnecessary. It is obvious that there are many such symptoms, in reaction to transient emergencies in everyday life, which never come to the attention of the physician. Symptoms, however, require explanation and a symptom may not be so easily dismissed after it has served its immediate purpose in solving the particular situation for which it appeared. With the attenuation of the external motivating forces which have brought the hysterical reaction to a head—attenuation brought about largely by the passage of time—we may find the patient in a situation in which he is just as anxious to escape *from* his illness as formerly he was anxious to escape *into* his illness. I am sure that situations just such as this account for many of the striking improvements noted after removal of perfectly benign appendices and tonsils, exploratory laparotomy, extraction of teeth and other more or less dramatic procedures, employed unwittingly to correct some somatized conflict symptom.

Clinical practice offers innumerable evidences of hysterical symptoms of sufficiently dramatic expression to demand the use of some equally dramatic therapeutic procedure with which at least to gain the patient's confidence. Although the indications for use of direct suggestion in therapy cannot be rigidly laid down, one does find that the outgoing, socially minded, physically healthy individual of average intelligence, but with less than average formal education, is more amenable to this type of treatment. The presence or development of true insight in these patients is minimal, but this may be said to characterize any hysterical reaction, short of that which is accorded prolonged analytic therapy. The patient who has the afore-mentioned attributes usually is subject to the *occasional* hysterical reaction rather than the *repeated* or *persistent* hysterical symptom, and in this respect offers an indication for the superficial, symptomatic treatment in the potentially transitory symptom.

Therefore, it would seem that there is a place for symptomatic treatment in the neuroses, just as there is justification for treatment of the common cold without extensive culture investigation in every case. The anamnesis should include a survey of the initiating or precipitating situations with the purpose of avoiding repetition of these ex-

posures, but it does not demand that there should be exhaustive investigation in every case to conform to the standards of acceptable medical practice

Some illustrative cases in which the type of therapy concerned herein was employed may serve to demonstrate the method and instances in which it can be utilized

REPORT OF CASES

CASE 1—A traumatic neurosis of a hysterical type occurred in a forty-two year old laborer, married and the father of four healthy children. He was first seen in October, 1939, at which time he complained of spasticity of the right leg that had followed an injury he had suffered eighteen months before when he was working at a pea-vining machine for a canning company. His clothes had been caught and he had been drawn into the machinery. He had been narrowly saved from a mutilating injury at the cost of a number of bruises, his clothing had been torn off his leg. The patient had collected compensation for about four or five months, then the insurance company had sent him to a physician who apparently had made a diagnosis of hysteria, administered physiotherapy and had told him he would be all right in two weeks. Supported by this medical opinion, the insurance company promptly ceased to pay compensation to him. The difficulty in walking persisted, however, and after about four months without compensation, the patient took his case to a lawyer who managed to reinstate the compensation as well as to force the insurance company to make up the lapsed payments. It was on the demand of the insurance company that the patient originally came to the Clinic for examination.

Objectively, results of the physical and neurologic examinations were essentially negative. There was an apparent right footdrop which, however, was somewhat bizarre, inasmuch as the patient experienced as much spasticity and difficulty in walking backward as he did in walking forward. It was decided to treat the patient by means of direct suggestion, with the use of faradic current stimulation as an initial approach, followed by constructive physiotherapy and psychotherapy. Particular care was taken to outline the patient's therapeutic program in terms of "saving his face," although from the beginning it was clearly explained to him that the anatomic structures of the leg were intact and that any physical injuries he may have suffered at the time of the accident were no longer directly responsible for his present symptoms. The patient was able to accept this well in terms of disordered function which, of course, he still attributed to the injury. After four days of the program of physical medicine which centered about stimulative electrical therapy, the patient was able to walk very well without the aid of crutches. It was explained to the insurance company that this did not represent primary malingering, and that it would be wise to allow him a few months additional compensation which would essentially carry him through the winter to the coming season that provided his chief source of income. The insurance company, in view of the unfavorable litigation in this case, was glad to make this concession. His improvement was well sustained six months later, when he was seen for re-examination as requested by the insurance company before the final settlement of the case.

Comment on Case 1—There may be certain arguments in this case for the diagnosis of malingering, inasmuch as the patient did not become well when there was great disadvantage in doing so, that is,

during the winter season of unemployment. It is for reasons such as this one that aspects of malingering are admitted by many psychiatrists, and because of this admission, a more or less punitive attitude may be taken by the physician who sees such a patient. When it is considered, however, that a hysterical reaction solves a problem involving social as well as personal features and that cure of a personal symptom, leaving a more critical social symptom unsolved is no cure at all, then it can be seen how the protective psyche can maintain a symptom indefinitely, or at least until environmental forces are more favorable to symptom change. These features are obviously operative on an unconscious level which is sufficient to exclude at least a primary malingering reaction.

CASE 2—A twenty-two year old single man, a farmer by occupation, had his right knee squeezed between the bumper of a car and a fence. A moderate amount of swelling and a little bruising resulted, these were sufficient to incapacitate him for about two weeks, during which time he kept the leg completely immobilized on the attending physician's orders. After this period and when it became time to try some activity, there appeared to be some swelling of the calf of his leg. At this time, a stocking type of anesthesia, with complete loss of motor function, was noted. It was in this condition that the patient was seen the early part of February, 1941, about five weeks after the injury.

The patient's general condition was good. Aside from the stocking distribution of the defect in sensory and motor function, results of the neurologic examination were entirely negative. The reflexes, including the deep tendon reflexes of the lower extremities, were essentially equal and normal. It was interesting to note that plantar stimulation elicited a normal plantar flexor response on the unaffected side, whereas similar stimulation on the right extremity, which was the affected one, elicited no response whatsoever. This reflex returned essentially to normal with a plantar flexor response after treatment. Allen mentions this phenomenon as a feature of some cases of hysteria. The inhibiting force of the psychologic reaction in this case was sufficiently powerful to immobilize the reflex whereas these reactions are usually normal in psychogenic disturbances. At the time of the patient's admission, the family's concern was remarkable, it was apparent that more than just the patient's reaction required treatment. Two or three members of the family, all simple farmer folk, asked if it would be necessary to amputate the extremity concerned, in spite of the assurance of their local physician that everything was "going to be all right" eventually. Although there had been no remarkable evidence of hysterical episodes of such a dramatic character occurring in this boy's history, it was evident that the patient was a simple-minded, suggestible individual of limited intellectual endowment who would not easily acquire any remarkable insight into the development of his illness. Investigation of his background revealed certain conflicts in respect to his loyalty to his family, to whom his services of labor were important. He was the oldest of three sons but since no privileges were granted to him over his younger brothers who also were helping on the farm, he felt that little evidence of appreciation of his own services was shown. Furthermore, he was anxious to be married and break away from home, but any mention thereof met with resistance from the family. The patient's illness served to show that the family could get along without his services, but probably most of all, his illness operated to satisfy his need for sympathy, attention and affection from the family, as well as to provide opportunity for his fiancée to play a more aggressive, protective role.

Comment on Case 2—This case, like the preceding one, shows a reaction which conforms with Schilder's contention that the cause of hysterical difficulties in men most often is found in social conflict and trauma. In this case, and in the preceding one, social factors were beginning or had already begun to place stress on the need of the patient to get well which, however, the protective psyche could permit only through graceful exit from illness.

So far as I am able to judge, neither of the patients could be considered eligible for psychoanalytic treatment in terms of intellectual, social and economic status, or difficulties of time and distance. Yet neither could a dictum of "You're all right, just forget about it," be expected to satisfy the patient (as the insurance company learned at considerable cost in the first case), since such an approach closes rather than opens the door for the graceful exit from illness.

COMMENT

It should be emphasized that the danger of the patient's interpretation of any dramatic procedures in terms of magic is ever-present. Consequently, repeated explanations should be made to the patient as to the integrity of his structural status, and that the treatment procedures are employed to demonstrate objectively the capacity of the affected organ for normal function, to initiate continuity of that function and to restore the patient's confidence in performance. This serves to negate the tendency toward a belief in mysticism or in any special powers of the physician, which idea is held by the relatively simple-minded individual who employs the hysterical conversion reaction to solve his conflict. This approach is not so dramatic as is the "Trust in me, I-will-cure-you" technique, but it is essentially honest, it supplies the patient's need, and the results are infinitely better in terms of sustained improvement.

In the administration of any therapeutic means of the suggestion type, it is important that such administration not be too closely identified with the physician who supervises the patient. In my experience, some form of electrical procedure such as faradic or sinusoidal wave stimulation or other form of electrical active physical therapy is best administered by someone other than the initial medical consultant. Such a course has shown far better results than those obtained when the physician plays the active role throughout all treatment contacts.

That is to say, there should be an apparent break in therapeutic continuity to impersonalize the treatment and to prevent a dependent, worshipful, emotional attachment of the patient to the physician. Such a change in therapists serves to speed the process of education of the patient to stand by himself without leaning on the symptom relieving physician.

Since hysterical symptoms are defensive and protective, there is danger of antagonism being directed against the physician, should he allow himself to be drawn into the patient's emotional milieu as substitute protector and then fail to satisfy the exacting, impatient demands put on him

SUMMARY

The use of suggestion therapy in hysteria warrants consideration as a technic of expediency and control of symptoms in selected patients. This technic is applicable in the simple conversion reaction occurring in the patient of limited intellectual endowment who is subjected to acute and probably transitory situational factors which often are precipitated by traumatic incidents. Frequently, the situational factors motivating the reaction are so attenuated by the lapse of time that the patient, when he seeks the counsel of his physician, is as desirous of release from his symptoms or symptom as he was initially desirous of escaping into illness to solve the acute problem. It is assumed that the physician has some understanding of the mechanism of conversion, that he will avoid an attitude of criticism and derogatory approach, and that he will provide the patient with an opportunity for a *graceful exit* from the symptoms. The symptom should be managed with reassurance to the patient in respect to the structural integrity of the affected organ, so that any sense of surrounding mysticism is dispelled.

Actual treatment is best carried out by some therapist other than the original supervising physician, so that emotional dependence of the patient on the physician may be avoided.

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CONVULSIVE DISORDERS IN CHILDREN

HADDOW M KEITH

To any physician practicing among children it is self evident that convulsive disorders are common and that the affected patients need treatment, frequently of an emergency nature. In addition, since generalized convulsion is frightening, the parents or guardians of affected children need reassurance and help in treating the immediate difficulty and in trying to prevent its recurrence.

It is a truism to state that in order to treat a patient effectively the cause of his difficulty must be understood. Although convulsive disorders necessarily have been recognized throughout the centuries, their ultimate causes are not yet known. During recent decades many important studies have been made, however, and with the aid of physico-chemical, electrophysical and careful clinical methods, the causes undoubtedly will be made clearer and a more logical approach to treatment will be possible.

It is an interesting and probably a scientifically healthy fact that widely divergent views in regard to the origin of convulsions and epilepsy are held by different workers. Buchanan said "There is no known difference in any one convulsion from any other, no matter whether it is associated with any recognized disease or not. The true pathogenesis of any convulsion is still unknown to medicine and there is no known cellular pathology for a convulsion itself. A convulsion, solitary or repeated, is a symptom and not a disease."

Peterman¹⁴ however, in considering convulsions and epilepsy said "Idiopathic epilepsy is the most common cause of recurring convulsions in childhood. . . The typical electroencephalograms of petit mal, the variants of petit mal, the psychomotor equivalent, and grand mal epilepsy confirm the contention that essential epilepsy is a disease entity and not merely a manifestation of the convulsive state. The terminology is of no consequence. The attempt to relegate essential epilepsy from a disease entity to another manifestation of the convulsive state is futile and would hinder the study of the disease."

Until the exact cause of convulsions is known, it is well to have a tentative classification of the various types. Penfield and Erickson classified them in three ways. (1) clinico-anatomically, (2) etiologically and (3) chronologically, that is, according to age of the patient at the onset of the convulsions.

McQuarrie has classified convulsive disorders on an etiologic basis. The classification in table 1 is a modification of McQuarrie's classification.

tion. In 1934, Peterman¹³ made a study of the causes of convulsions in a series of 500 cases in which the patients were children. He recently has reported the results of a study of a larger series of 2,500 cases

TABLE 1
ETIOLOGIC CLASSIFICATION OF CONVULSIVE DISORDERS

- I Acute or nonrecurrent convulsions
 - a. Extracranial infection.
 - b. Intracranial infection.
 - c. Intracranial hemorrhage.
 - d. Toxemia
 - e. Anoxia.
 - f. Metabolic disturbances.
 - g. Acute cerebral edema.
 - h. Tumor of the brain.
- II Chronic or recurrent convulsions.
 - a. Epilepsy.
 - b. Pyknolepsy
 - c. Narcolepsy and cataplexy
 - d. Hysteria.
 - e. Tetany
 - f. Hypoglycemic states
 - g. Uremia.
 - h. "Cerebral" allergy
 - i. Cardiovascular dysfunction
 - j. Parasitic disease of the brain.
 - k. Intracranial neoplasms
 - l. Migraine.

The causes of the convulsions in these cases are shown in table 2. He pointed out that there was a striking correlation between the results in his first series and the results in the later and larger series

TABLE 2
CAUSES OF CONVULSIONS IN 2,500 CASES
REPORTED BY PETERMAN¹⁴

Cause	Cases, per cent
Acute infection	33 4
Idiopathic epilepsy	26 3
Cerebral birth injury or residua	14 2
Miscellaneous causes	13 1
Infantile tetany	7 4
Unknown	5 6

No article on convulsive disorder would be complete without a consideration of electro-encephalography and encephalography. The latter is a valuable procedure in cases in which the presence of a gross cerebral anatomic lesion is suspected. Combined with other clinical methods, it is most important in the study of atrophic and cicatricial

that this objective is not always attained. The only alternative to irradiation is the enucleation of both eyes.

Inasmuch as there may be a considerable lapse of time between the appearance of the tumor in one eye and in the other, a child must be examined regularly for many years following the treatment of his initial lesion. The familial tendency of this cancer has been mentioned by numerous authors and in the Memorial Hospital cases there have been two such instances.

Prognosis.—In many instances this tumor does not metastasize for many months after its first appearance. We have had cases without metastases for twelve months after onset of the initial symptoms. Again, cases in this group have metastasized within a few months after the apparent clinical inception of the disease.

The longest survival period in a bilateral case among our patients was in a child who had an enucleation of one eye plus irradiation of the other eye. There was no evidence at her most recent examination (July, 1946) of recurrence or metastasis, thirteen years after her initial treatment.

TUMORS OF THE BONES

Malignant tumors arising from bone are seldom encountered before the fourth year of life. However, soft part tumors such as liposarcoma and fibrosarcoma, which may secondarily involve bone, not uncommonly occur very early in life and have been noted even at birth.

Many bone tumors present difficulties in diagnosis and differential diagnosis not only during their early stages but sometimes after the disease has been present for a considerable period of time. The tumors not only may show roentgenological similarities to one another but may also resemble diseases of a non-neoplastic nature. It is important, therefore, that complete clinical data, namely, age, history, physical findings, course of the disease, and the laboratory findings, be carefully studied and evaluated before arriving at a diagnosis. In many instances the great emphasis placed on roentgenologic changes is justified but if x-ray studies are used as the sole diagnostic criterion, errors will be made in some cases. The pathologist, too, may occasionally be unable to render a correct diagnosis on biopsy specimens. If all the findings, however, are assayed in each case, it will seldom be necessary to resort to biopsy to differentiate a bony neoplasm from such diseases as syphilis, tuberculosis, scurvy, xanthomatosis, rheumatic infection, parathyroid disease, osteomyelitis and fracture, with which bone tumors are frequently confused.

Pain is one of the earliest subjective symptoms of bone cancer but is not common in the benign tumors. Impaired function is rare in the benign neoplasm until the growth reaches a considerable size. Fever is not infrequently noted in bone cancer.

lesions, as demonstrated by Penfield, and Penfield and Keith, both in confirming the presence of a focal lesion and in indicating the point of attack in surgical treatment

Electro-encephalography, which originally was described by Berger, has opened a new field for the study of epilepsy and convulsive disorders. In the past decade, many workers have made valuable contributions to this subject. Gibbs and Gibbs have graphically described the various tracings recorded from normal persons of all ages and from persons with convulsive and other disorders. Jasper has described in detail normal and abnormal waves and rhythms. Electro-encephalography of the normal adult brain reveals four types of rhythm, namely, alpha, beta, gamma and delta. These rhythms are not present or are not fully developed in electro-encephalograms of persons who are less than eight to twelve years of age.

Variations in these rhythms commonly are observed in cases of convulsive disorders. Electro-encephalography is being used more and more in the diagnosis and study of convulsions. It undoubtedly will be of considerable value in elucidating the mechanism of convulsive phenomena. Since electro-encephalography is a laboratory procedure that is not infallible, the results should be evaluated with caution and judgment. Gibbs, Gibbs and Lennox found that 13 per cent of a large group of epileptic patients had normal electro-encephalographic rhythms. These investigators found that routine electro-encephalography is of diagnostic value in 48 per cent of cases in which there is a history of epileptic convulsions.

TREATMENT OF CONVULSIONS

In order to treat convulsive disorders most effectively, an attempt should be made to determine the underlying cause. In this connection, it should be remembered that more than one cause may be present in an individual case. Emergency treatment frequently is necessary in cases of convulsions.

It usually is difficult or impossible to stop a single convulsion but a series of convulsions may be treated effectively by medical or physical agents. As a rule, a general anesthetic agent produces the best results. Since ether usually is readily available and its action is well known, this is the agent of choice. The barbiturates, which may be administered intravenously, subcutaneously or rectally, also are satisfactory.

Pentothal sodium (sodium ethyl [methylbutyl] diobarbiturate) is administered intravenously for its immediate effect. As a rule, this drug is not given to children less than ten years of age in connection with operations, however, in an emergency, small doses of the drug may be given. An initial dose of 1 cc of a 2.5 per cent solution may be administered and subsequent doses of 0.5 to 1 cc may be ad-

ministered at intervals of ten to fifteen seconds until the convulsion is controlled. At the same time, the rectal administration of pentobarbital sodium in doses of $\frac{1}{2}$ to 3 grains (0.032 to 0.2 gm) should be started. This drug should be administered frequently enough to prevent further attacks until the underlying causative condition has been corrected and there is no likelihood of further attacks.

Sodium amytal (sodium iso-amylethyl barbiturate) has been administered intravenously as a 5 per cent solution (5 mg of sodium amytal per kilogram of body weight) at a rate not exceeding 1 c.c. per minute. Its action is somewhat slower than that of pentothal sodium and its effect is more prolonged.

The rectal administration of solution of tribromethanol in the usual basic anesthetic dose of 0.075 c.c. per kilogram of body weight also has been effective in controlling a series of convulsions. A dose of 0.025 to 0.05 c.c. per kilogram of body weight may be repeated every four to six hours if necessary. Each cubic centimeter of solution of tribromethanol contains 1 gm of tribromethanol in amylene hydrate.

Another effective agent for rectal administration is chloral hydrate. This may be given every two to four hours in doses of 3 to 15 grains (0.2 to 1 gm) depending on the age of the patient.

At times magnesium sulfate has been effective, especially in the control of convulsions caused by acute nephritis. A 10 to 25 per cent solution of this drug is administered intramuscularly. The rectal dose of magnesium sulfate is 0.2 gm per kilogram of body weight. This dose may be repeated every four to six hours if necessary.

Oxygen given by means of a tent or mask is sometimes effective in controlling a series of convulsions, particularly if cyanosis is present. It may be used in conjunction with any of the previously described drugs. In certain cases, removal of a few cubic centimeters of spinal fluid may prove beneficial. This procedure is not without danger in cases of increased intracranial pressure.

Treatment of Special Types of Convulsions.—*Acute Infectious Diseases*—Convulsions commonly occur at the onset of an infectious disease in a young child. Since such an attack may be dependent on high fever, measures to reduce the temperature, followed by specific treatment, if possible, should be undertaken. The administration of an enema prepared with cold tap water or even ice water is of considerable help. After this the body may be sponged with tepid water or a tepid pack may be applied. These measures may be followed by the administration of acetylsalicylic acid. The administration of anticonvulsant drugs usually is unnecessary unless a series of convulsions occurs.

Tumor of the Brain—Relief of pressure by operation is imperative when a tumor of the brain is present. Tumor of the brain is a relatively uncommon cause of convulsion but the physician should keep in

mind the cardinal symptoms and signs. These are headache, vomiting, ataxia, swelling of the optic disks and roentgenologic evidence of increased intracranial pressure such as separation of sutures in the skull.

Congenital Cerebral Defect—General anticonvulsant measures are useful in the treatment of convulsions due to a congenital cerebral defect. No treatment of the defect is possible.

Congenital Syphilis—General measures, as previously outlined, followed by antisyphilitic treatment, should be instituted for convulsions caused by congenital syphilis. This condition is rarely encountered at the Clinic.

Direct Trauma—In cases of concussion only, with no evidence of fracture, hemorrhage or laceration, general measures for control of convulsion may be used. Direct trauma is essentially a surgical condition.

Gastro-enteritis—The fever or toxemia that is associated with gastro-enteritis probably is the cause of the convulsions. Treatment is the same as for convulsion caused by acute infectious disease. Since dehydration is usually present, adequate amounts of fluid should be supplied.

Hydrocephalus—The diagnosis of hydrocephalus is dependent on abnormal enlargement of the head, an excessive amount of cerebrospinal fluid and enlargement of the ventricles. In external hydrocephalus, the enlargement is due to fluid outside the ventricles. Convulsions caused by either internal or external hydrocephalus should be treated by general measures, followed by surgical treatment of the underlying condition if possible.

Intracranial Abscess—Diagnosis of intracranial abscess is usually difficult. The presence of such a condition is suggested by evidence of infection and of focal involvement of the nervous system. Treatment consists of general measures to control the convulsions. This should be followed by surgical treatment of the abscess.

Intracranial Hemorrhage—Convulsions, either focal or general in type, may be the result of hemorrhage due to injury at birth or to any gross injury of the head. If the bleeding is due to birth injury, oral or rectal administration of chloral hydrate in doses of 1 to 3 grains, (0.065 to 0.2 gm) or rectal administration of pentobarbital sodium in doses of $\frac{1}{4}$ to $\frac{1}{2}$ grain (0.016 to 0.032 gm) may be tried. Magnesium sulfate administered intramuscularly also has been satisfactory.

If the fontanel is tense, spinal drainage may be indicated. Objections to this procedure have been raised on the basis of the fact that it disturbs the patient and the lowering of the intracranial pressure increases the tendency to hemorrhage. The administration of oxygen because of a tent frequently is indicated. Menadione (2-methyl-1,4-naphthoquinone) may be administered intramuscularly in daily doses of 15 to 30 mg. for seven to ten days.

If the hemorrhage is due to direct trauma, particularly if the middle meningeal artery has been ruptured, surgical treatment is indicated

Meningitis—Convulsions due to meningitis require immediate treatment by general measures, followed by active treatment of the meningitis

Strychnine Poisoning—Because of the prevalence, in homes, of preparations containing strychnine, convulsions due to this drug are not an uncommon occurrence. In spite of all precautions, children obtain and take strychnine, and generalized convulsions develop rapidly. The diagnosis usually is suggested by the history which discloses that the patient swallowed excessive amounts of either a tonic or pills before the occurrence of generalized tonic convulsions. The following immediate treatment, in the order mentioned, has proved effective: (1) intravenous administration of pentothal sodium, as previously described, (2) insertion of a tracheal catheter to overcome the laryngeal spasm and subsequent administration of oxygen by means of a mask or tent and (3) rectal administration of pentobarbital sodium, $1\frac{1}{2}$ to 3 grains (0.1 to 0.2 gm). The administration of pentobarbital sodium should be repeated frequently enough to prevent the recurrence of convulsions for twelve to twenty-four hours or until there is no danger that the convulsions will recur.

Convulsions may be due to many other poisons. Because of the extensiveness of the subject of poisoning, it will not be considered further in this paper.

Tetanus—At the Clinic, we see very few cases of tetanus. The prophylactic use of antitoxin in the treatment of contaminated wounds undoubtedly has been a major factor in reducing the incidence of tetanus to a minimum. In addition, active immunity may be produced by the use of tetanus toxoid; this method of prophylaxis has proved satisfactory in Army practice. However, when convulsions occur suddenly and without obvious cause, the possibility of tetanus must be considered, and a search for a focus of infection, however small, should be made.

In treating the patient, all stimuli must be reduced to a minimum. The child must be kept in bed in a darkened room and handled as little as possible. Feeding may be carried out by means of a nasal tube, and dextrose and saline solutions may be administered intravenously by the continuous drip method.

Solution of tribromethanol has been found effective in controlling convulsions caused by tetanus. The usual anesthetic dose of this preparation, which is 0.075 cc per kilogram of body weight, may be administered rectally. This may be followed at intervals of one to three hours by administration of 0.01 to 0.015 cc per kilogram of body weight.

Sodium amytal may be administered intravenously and pento-

barbital sodium also may be used. The use of these drugs has been described previously. Intocostrin* has been administered intravenously or intramuscularly. Cullen and Quinn administered approximately 0.05 gm. of intocostrin every three hours to a man who had tetanus. The drug should be administered often enough, and in doses that are large enough, to relieve the pain and muscle spasm.

A large dose of antitoxin should be administered as soon as possible after the occurrence of a convulsion caused by tetanus. Calvin recommended the following method of treatment. After it has been established that the patient is not sensitive to horse serum, 50,000 units of tetanus antitoxin are added to 500 c.c. of physiologic salt solution at body temperature. The resulting solution is administered intravenously at the rate of 60 drops per minute. If a chill occurs, the intravenous administration should be stopped and the remaining portion of the solution should be administered intramuscularly. An additional 50,000 units of the antitoxin should be administered intramuscularly. Holt and McIntosh advised that the primary wound should be excised and that antitoxin should be administered no matter how much antitoxin previously had been administered.

Tetany—Convulsions in infants and small children who are less than three years of age sometimes are caused by tetany, which usually is associated with some degree of rickets. Such convulsions are particularly dependent on a low concentration of serum calcium. In many cases, the value for the calcium is less than 8 mg. per 100 c.c. of serum. Chvostek's sign is present.

Convulsions due to tetany may be generalized and may be indistinguishable from convulsions due to other causes. They may be controlled by one of the following methods. A 10 per cent solution of calcium gluconate may be administered intravenously or intramuscularly, in doses of 10 c.c. every four to six hours. Sloughing occasionally may occur after intramuscular injection. Calcium chloride may be administered orally or intravenously. The latter method must be used with care since injection of the solution outside a vein may cause sloughing. When calcium chloride is given orally, the initial dose is 15 to 60 grains (3 to 4 gm.). It should be administered in the form of a 10 per cent solution in water or milk. This is followed by administration of doses of 15 grains (1 gm.) three or four times daily. Twenty-four hours after the administration of calcium has been started the

* According to New and Nonofficial Remedies, 1946, intocostrin is a preparation containing therapeutically desirable constituents of curare. The curare activity of this preparation is due almost entirely to the presence of d-tubocurarine. The preparation usually is administered in the form of intocostrin solution. The solution is standardized so that 1 unit has the activity of 1 mg. of the standard d-tubocurarine (intocostrin). Each cubic centimeter of intocostrin solution contains the equivalent of 20 units of intocostrin.

administration of cod liver oil or another preparation of vitamin D should be started and continued indefinitely. Chloral hydrate may be given orally or rectally. Three to 5 grains (0.2 to 0.3 gm) may be given to infants less than six months of age and 5 to 10 grains (0.3 to 0.65 gm) may be given to children more than six months of age. In some cases of convulsion, the administration of ether may be required.

Uremia—Uremia or pseudo-uremia in the course of nephritis may precipitate convulsion. When the blood pressure is elevated, uremia may develop regardless of whether retention of nitrogen is excessive. Under such circumstances, drowsiness or vomiting, with the onset of coma, may be accompanied by generalized convulsions.

Uremic convulsions may be treated by any of the methods previously outlined under emergency treatment. Lumbar puncture is one of the methods of choice. Some authors recommend, in addition, the use of morphine. A 2 per cent solution of magnesium sulfate should be injected intravenously, at a rate not faster than 2 c.c. per minute, until the blood pressure returns to normal. After the convulsions have ceased and the patient is no longer in a state of coma, large doses of saturated solution of magnesium sulfate should be administered by mouth until the blood pressure is stabilized. The patient should be urged to take large amounts of fluids.

Epilepsy—The treatment of recurring convulsions (epilepsy) has been and still is a difficult problem, since there are so many variables and since treatment must be continued for a long period. The causation of such convulsions is, of course, extremely important. Unfortunately, in the majority of cases the cause of the attacks cannot be determined with accuracy, and the physician is forced to treat the symptom without being certain of the underlying pathologic disturbance. Even when the latter can be recognized, it is frequently impossible to remove or alter the fundamental abnormality, therefore, treatment again must be directed toward the symptom.

It is undoubtedly necessary that mental hygiene be considered in the treatment of epileptic patients. In certain cases there are emotional and mental stresses which may well be precipitating factors in the attack. Repeated discussions with parents or other members of the patient's family may disclose mental conflicts and anxieties not otherwise noted. A tactful social worker or a schoolteacher who is in close contact with the family may render valuable service in this direction.

It is frequently a question whether a child who has epilepsy can or should remain in school. This will, of course, depend to some extent on the frequency and severity of the attacks. If they are rare, or are well controlled by drugs or diet, it is advisable for the child to

remain in public school. If the attacks are more frequent or severe, it undoubtedly is well to have the child in a special school for epileptics or even in an institution. His education, however, should proceed as nearly normally as possible, so that he will not feel that he is "different" from other children. His social environment and activities should be as nearly as possible the same as those of a normal child.

Although perhaps not all workers will agree, it is generally considered that an epileptiform attack is due to an "explosion" of abnormal impulses in some portion of the brain, causing disorderly responses in the neuromuscular mechanism, frequently accompanied by an interruption of the conscious processes in the cerebrum. This presupposes an abnormal irritability of a portion or portions of the cerebral mechanisms. Most forms of treatment have been directed toward reducing this increased irritability and the resulting "explosion," and drugs which have a sedative or "anticonvulsive" but not a soporific action have been most frequently used. The object of treatment is the complete prevention of seizures, with as little interference as possible with mental and emotional development as well as physical activity.

The bromides were among the earlier and more successful drugs used in this manner. Charles Laeock reported their use as early as 1853. In writing of the bromides in 1883, Gowers said "In the majority of cases their influence is incomparably greater than that of any other remedies. They only do permanent good by continued administration."

The next drug to come into prominence (1912) was phenobarbital, which is relatively nontoxic and reasonably effective. It is probably the most widely used anticonvulsive agent at present. Later, mephobarbital (methylethylphenyl barbituric acid), which is closely related to phenobarbital, was introduced. In 1938, Merritt and Putnam reported on the administration of dilantin sodium (diphenylhydantoin sodium). This agent has been used rather extensively. All these drugs have been found to be most effective in the treatment of the grand mal or generalized convulsive type of disturbance, but much less effective in the control of the petit mal or momentary type of attack. Within the past two years tridione (3,5,5-trimethyl-2-oxo-1,4-dioxane-6-carboxylic acid) has been found to be comparatively effective in the control of attacks of petit mal, and for this purpose it appears to have considerable superiority over the older drugs. This substance can be used in combination with any of the other drugs, and such a combination may be very effective when both types of attack occur. Recently, it has been reported that tridione may cause agranulocytosis and death. In 1947, Clein and later Kozol reported the use of another new anticonvulsive drug, phenacemide or mesacemide. It is administered in tablet form. Although the early reports on the use of this drug have been favorable,

able, it remains to be seen whether it will be more useful than other drugs

All the anticonvulsive drugs should be administered in doses sufficient to accomplish the desired purpose, namely, suppression of the attacks, but not in sufficiently large doses to cause symptoms of toxicity. It is common practice to begin with a minimal dose and to increase it gradually until the attacks cease, or until signs of toxic effect appear. When the correct dose has been determined, administration of the drug should be continued for a period of one year to five years. The dose may then be very gradually decreased until administration of the drug finally is discontinued.

In addition to drugs, a ketogenic diet has been shown to be an effective method of treatment for children who have grand mal or petit mal or both. The ketogenic diet, to be effective, must be rigidly controlled, and the constituents should be weighed. It is necessary that in the diet the ratio of the ketogenic material to the antiketogenic material be at least 3:1. This ratio is calculated according to Wood-yatt's formula in the following manner:

$$\begin{array}{rcl}
 \text{Ketogenic material} & \text{--} & 90 \text{ per cent of fat} \\
 & & 46 \text{ per cent of protein} \\
 \text{Antiketogenic material} & \text{--} & \text{All of carbohydrate} \\
 & & 58 \text{ per cent of protein} \\
 & & 10 \text{ per cent of fat} \\
 \\
 \frac{\text{Ketogenic material}}{\text{Antiketogenic material}} & \text{or} & \frac{\text{Fatty acid}}{\text{Dextrose}} \\
 & \text{ratio is} & \\
 & 0.90\text{F} + 0.46\text{P} & \\
 & \hline & \text{C} + 0.1\text{F} + 0.58\text{P}
 \end{array}$$

The diet is then calculated for the individual patient as follows. For children, the number of calories is 55 per kilogram, or 25 per pound of body weight (table 3). The amount of protein is set at 1 gm. per kilogram of body weight, which has been found to be very satisfactory. The amounts of carbohydrate and fat are then adjusted so that the ratio is as indicated and the calories are satisfactory for nutrition and growth. The caloric requirement is based on the estimated weight for height, as given in standard tables.

In a period of four days the content of carbohydrate in the diet decreases rapidly and that of the fat increases. This is advisable because most children placed immediately on the final diet will become nauseated and sometimes will experience severe vomiting. However, when the plan indicated is used, this very seldom occurs. To make certain that the patient is in a state of ketosis, a test for diacetic acid is performed daily on the first morning specimen of urine. The patient's mother can be taught to perform such a test readily. Patients

must subsist on this diet, in a state of ketosis, for from six to twelve months. The amount of carbohydrate in the diet then is increased gradually and the amount of fat is reduced until the diet is essentially normal again. This usually takes place over a period of three to six months. The diet for an adult person is the same in principle, although the caloric demand and the amount of protein necessary are different.

In an attempt to evaluate drug therapy and treatment with the ketogenic diet, records of 300 consecutive epileptic children first examined in 1940 and 1941 were studied. The patients were classified in three ways: (1) *well* patients who had had no attacks of any kind so far as they knew from the time of the beginning of the treatment

TABLE 3

KETOGENIC DIET TOTAL GRAMS OF CARBOHYDRATES, PROTEINS AND FATS REQUIRED IN FOUR DAYS* BY A BOY EIGHT YEARS OLD WEIGHING 55 POUNDS (25 Kg.)

Day	Carbohydrates, gm	Proteins, gm	Fats, gm	Calories	Ratio, Ketogenic Material to Antiketogenic Material
First	50	25	119	1,371	1.5
Second	35	25	126	1,374	2.0
Third	20	25	133	1,377	2.7
Fourth	15	25	135	1,375	3.1

*A child requires 25 calories per pound of body weight or 55 calories per kilogram of body weight.

or shortly thereafter until the end of the follow-up period (between four and five years), (2) *improved* patients who had shown definite improvement either for a comparatively short time or for a much longer time, but who still had some difficulty, and (3) *not benefited* patients who had continued to have attacks in spite of reasonable treatment.

No follow-up information was obtained in 113 of the 300 cases. Of the remaining 187 patients thirty-eight had gross neurologic disturbances such as cerebral palsy, marked mental retardation and hydrocephalus. Seventeen of these patients improved, as far as their attacks were concerned, eight of them improved after treatment with phenobarbital alone, four improved after treatment with dilantin, and three improved after treatment with a combination of these two drugs, one improved as a result of the ketogenic diet. One patient

became well without any treatment and remained so for four years. Two of the children in this group died while they were undergoing treatment, one died of general paresis and one died of rather severe hydrocephalus. There were 177 patients who had no gross handicap except the convulsions, and it is fair to consider that they had had good treatment for four to five years.

Thirty-seven patients were treated only by means of the ketogenic diet. Of these, ten remained completely well, sixteen were improved, and eleven were not helped. A group of fifteen patients were treated by means of the ketogenic diet plus drugs. Four of these patients remained well, three were improved, and eight were not helped.

The ketogenic diet was used until the patient had been free of attacks for one year or more, when it was gradually changed to a normal diet, usually with a moderately limited amount of carbohydrate. When drugs were used in addition to the diet, their administration generally was continued after the change in diet had been made.

Forty-eight patients received phenobarbital alone. Of these, six remained "well," but continued to take full doses of medicine. Thirty-one improved for periods varying from a few months to four years.

Fifty patients received dilantin sodium alone. Six remained well (while taking the drug), nineteen were improved, and twenty-five obtained no relief. It is interesting to note that twelve patients of this group had toxic reactions, they were the only patients who did have evidence of such reactions.

A final group of twenty-six patients received both phenobarbital and dilantin sodium. Three patients were well while taking the drugs consistently, twelve patients were improved, and eleven failed to obtain any relief.

It appears that in this group of 187 patients the ketogenic diet was the most satisfactory form of treatment. It must be remembered that, almost without exception, treatment with drugs previously had been ineffective.

The second group studied consisted of all patients given the ketogenic diet alone or the diet with drugs during the period 1921 to 1930. The records were studied up to and including 1945, thus giving periods of observation from twenty-four years to fifteen years. This group consisted of 311 patients. Seventy-three of these patients did not co-operate well enough to make it possible to determine whether the diet would help them or not. Forty-eight had gross neurologic lesions, including a tumor of the brain in one case. There were then 190 patients who gave the diet a fair trial. Sixty-seven patients remained well for from four to twenty-two years after the treatment was discontinued. A few of these patients have not been heard from in recent years. Some may have had recurrent attacks, but at least it is known that they were well for the periods stated.

BENIGN TUMORS OF THE BONES

Bone Cysts—The solitary bone cyst is most common in the humerus, femur and tibia. The diagnosis is rarely made until a pathologic fracture occurs. Roentgenographically an expansion appears in the metaphyseal area associated with central bone destruction and surrounded by a layer of thin cortical bone. Irregular trabeculations are seen in the cystic cavity.

Multiple bone cysts are frequently associated with hyperparathyroidism. A high serum calcium, low phosphorus, and an increase in alkaline phosphatase are considered diagnostic of this disease.

TREATMENT—Bone cysts are curetted and the cavity is filled with bone chips.

Chondroma.—The well known *osteochondroma* (exostosis) arises near the joints, frequently at the sites of tendon insertions.

TREATMENT—Chondromas seldom require surgical intervention unless they grow to an appreciable size or are located in a position which results in interference with normal function.

Enchondroma, a less common variety, is found most often in the phalanges, but may be observed in the femur, tibia or other large bone. Roentgenographically it appears as a radiolucent tumor, usually in the shaft, with relatively even striations throughout.

Giant Cell Tumor.—This tumor is not often encountered in childhood but occurs usually during adolescence after the shaft and epiphysis have united. It is recognized roentgenographically by a wide uniform shadow, well-marked trabeculations, giving, in many cases, a "quartzlike appearance" and characteristically involving the epiphysis.

It should be appreciated that chondromas and giant cell tumors sometimes assume malignant characteristics later in life even though apparently initially benign during childhood.

TREATMENT—Giant cell tumors are treated by curettage and bone chips or transplants, or by irradiation. The present policy at Memorial Hospital is to use irradiation if the tumor is inaccessible and surgery if it is accessible.

Osteoid Osteoma—This tumor occurs most frequently in the long bones. If located near the bone surface it sometimes causes considerable periosteal reaction and pain. Roentgenographically it is recognized by the following characteristics (Fig 61): (1) Dense cortical thickening, the length of which may be 2 cm to 10 cm. (2) Within this thickened area there is seen in most cases a radiolucent nidus (0.5 to 2 cm) which at times contains a small, slightly radiopaque center.

Onion-peel lamellations may or may not be present, depending on the proximity of the tumor to the periosteum. This neoplasm has been confused with Brodie's abscess, endothelioma, osteogenic sarcoma and osteomyelitis.

Thirty-five patients were definitely improved, so much so that they were willing to continue the diet for several years. One patient has continued the diet for nineteen years, although she was advised to discontinue it after three years. When asked why she continued the diet, this patient said that she had become used to it, that it was not difficult, and that she experienced attacks only rarely when she was adhering to the diet. Thus, by means of the ketogenic diet, 56.1 per cent of the patients with so-called idiopathic epilepsy have been influenced favorably, and 37.4 per cent have been "well" for long periods (up to twenty-two years).

The inheritance of epilepsy is a subject on which much has been written. It is not within the scope of this paper to consider this phase of the subject. Penfield and Erickson stated that "The conclusion can not be avoided that some potential or latent germ plasma defect or vulnerability is inherited." In this connection, it is of interest and perhaps of value to point out that among the 190 patients concerning whom follow-up studies were made, twenty gave birth to twenty nine children. The ages of the children at the time of this study ranged from a few months to twelve years. Not one of these children had been observed to have convulsions of any sort.

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HISTAMINE ANTAGONISTS IN THE TREATMENT OF ALLERGIC DISEASE IN CHILDREN

GEORGE B. LOGAN

WITHIN the past two years, several so-called histamine antagonists have been shown to be useful drugs. It is the purpose of this paper to consider the usefulness and shortcomings of two of these chemical compounds (benadryl and pyribenzamine) in the treatment of allergic diseases in children in the light of our recent experience.

In recent articles by Code and Feinberg the background for the use of the drugs in the treatment of allergic conditions is reviewed. It may be said here, however, that there is good experimental evidence that release of histamine or a similar substance (H substance) plays an important role in the production of the symptoms of anaphylactic shock. There is some evidence, also, that the release of histamine (or H substance) is equally important in human allergic disease. It is recognized, however, that histamine is not responsible for all of the allergic reaction. In the experimental laboratory the currently available histamine antagonists, at best, prevent only about 90 per cent of the symptoms of histamine shock. The histamine antagonists in some way block the allergic or histamine reaction, and contribute to its disappearance when it is already established.

It may be seen, therefore, that even theoretically it cannot be expected that complete relief of symptoms of allergic disease will follow the use of the drugs which are at present obtainable. However, a drug which will give 50 to 75 per cent relief from allergic symptoms usually is felt by the patients to be a useful drug. Our clinical results to date in the treatment of children with allergic diseases have been sufficiently encouraging to justify the employment of these or similar drugs. Active research continues in this field, and it is anticipated that new "antihistamine" compounds will be introduced. As the anti-histamine powers are enhanced and the untoward reactions are decreased, the newer compounds will displace the old.

It is well to emphasize, however, that the use of these drugs in the control or prevention of the allergic reaction is not a substitute for thorough investigation of the allergy in question. They are drugs which bring only symptomatic relief to some, but not all patients treated for allergic disease. They in no way immunize the child. Beneficial results which follow the administration of benadryl or pyribenzamine suggest that the disease treated may have an allergic basis or a similar mechanism of action. If no beneficial result occurs

it cannot, however, be concluded that the disease being treated does not have an allergic basis

Our experience has been limited to observation of the effect in children of the two histamine antagonists benadryl (beta-dimethyl-aminoethyl benzhydryl ether hydrochloride) and pyribenzamine (N'-pyridyl-N'-benzyl-N-dimethyl-ethylene diamine hydrochloride) Halpern, Bovet and others in France have reported their clinical and experimental experience with two other compounds antergan (N'-phenyl-N'-benzyl-N-dimethyl-ethylene diamine) and neo-antergan (N-p-methoxy benzyl-N-dimethyl-amino ethyl a amino pyridine) Another drug, as yet unnamed, has been reported by Halpern to exert approximately sixteen times the antihistaminic effect of neo-antergan These drugs are not yet commercially available in the United States Reports⁸ concerning antistine (2-[N-phenyl N-benzyl-amino ethyl] imidazolin) have appeared in the Swiss literature It, likewise, is not as yet available for clinical use in the United States

DOSAGE AND ADMINISTRATION

The principles of adequate dosage and suitable means of administration are very important in pediatric therapeutics Too large a dose of a drug must be avoided, and yet enough must be administered to obtain a therapeutic effect Often, those only slightly familiar with the use of these drugs have shown a tendency to administer too small a dose for children Our early experience with benadryl suggested that approximately 2 mg per pound of body weight constituted an adequate total twenty-four hour dose This amount is generally divided into three or four doses However, children less than five or six years old often require more than this We have administered up to 6 mg per pound of body weight in a twenty-four hour period, but not for more than one day Older children may not need the entire suggested amount It is necessary, at times, to administer benadryl and pyribenzamine at more frequent intervals

Often, we have found that a dose of pyribenzamine smaller than that of benadryl suffices Both drugs may benefit a child, though sometimes one and sometimes the other is effective Sometimes neither drug is of value When two boys, nine and twelve years old, who had vasomotor rhinitis were being treated, 50 mg given three times daily was without effect, but the same amount given five times daily, produced a favorable effect.

EFFECTS IN GENERAL

Favorable Effects.—The favorable effect is prompt if an adequate dose has been administered Rarely does one have to wait longer than an hour to observe it In some instances, especially when the drugs have been ingested when the stomach was empty, effects have been

noted within ten to fifteen minutes. The duration of the beneficial effect has varied from ninety minutes to nearly twenty-four hours.

Untoward Effects.—Various observers have noted untoward reactions to the use of benadryl and pyribenzamine in 25 to 80 per cent of cases. Our experience with children has been that the reactions occur in 25 to 30 per cent of cases, and that they are sufficiently undesirable to cause discontinuance of use of the drug in about 10 to 15 per cent of cases. One author³ recently has suggested that since some of the untoward reactions, particularly drowsiness, occur so frequently, they should be considered to be a part of the action of the drugs. His contention that the favorable effect of the histamine antagonists is not dependent on the antihistamine action, but on a sedative action, remains to be proved.

We have encountered the following reactions: drowsiness, vomiting, diarrhea, nausea, headache, tachycardia and hematuria. Except for drowsiness and vomiting, only single instances of these effects have been noted.

Other undesirable reactions noted by other workers are dizziness, dry mouth, feeling of nervousness, insomnia, epigastric distress, dermatitis, difficulty in co-ordination and dilatation of the pupils and also asthma, urticaria, collapse, muscular aching and acute melancholia. Leukopenia has not been reported to follow the use of benadryl or pyribenzamine, but it has followed the use of antergan. It would seem desirable to carry out periodic erythrocyte and leukocyte counts among children who are receiving these drugs for a prolonged period, such counts probably should be made at least every six to eight weeks.

Drowsiness is not an undesirable reaction when these drugs are administered at night. In some patients, the concomitant administration of caffeine and sodium benzoate or benzedrine in small doses has been reported to have overcome this side effect. One observer³ has reported the successful use of 25 mg. of pyridoxine or 50 mg. of niacinamide daily for the same purpose.

Recently, we admitted a two year old boy to our hospital service because of the sudden onset twelve hours before of irrational behavior. He had hallucinations and attempted to pick things out of the air. After several hours of this sort of behavior, he went to sleep and seemed entirely normal on awakening some time later. Results of a complete neurologic examination were normal. The boy told his parents that he had ingested a capsule from the medicine cabinet. The capsule contained 50 mg. of benadryl. A somewhat similar instance recently was reported by Weil.

The question of habit formation or addiction has been raised by some physicians. We have had no such experience with children. However, I do not think that these drugs are designed for an indefinite period of administration. Some physicians have noted that the sudden

stopping of administration of one of the antihistamine drugs to a patient in the midst of a pollen season seems to precipitate a severe attack of the type of allergic disease from which the patient suffers

SPECIFIC CONDITIONS

Asthma.—There is considerable difference of opinion regarding the value of the histamine antagonists in the treatment of asthma. We feel that for children these antagonists are useful additions to therapy. It is generally agreed, however, that patients suffering from chronic asthma, especially if emphysematous changes are present, are rarely if ever benefited from the use of these drugs. A few patients suffering from what appears to be uncomplicated asthma seemingly are helped by the use of benadryl or pyribenzamine. Among children, we have often found that the concomitant use of one of these drugs with a saturated solution of sodium or potassium iodide is more effective than the use of either drug alone. Administration of this combination should be started at the first sign of an impending attack, since such a procedure utilizes the liquefying action of the iodides on bronchial secretions and the bronchodilating and antihistamine actions of benadryl or pyribenzamine. Children in whom wheezing develops whenever they contract a respiratory infection often are greatly relieved by the use of one of the antihistamine agents throughout the course of the infection. If these drugs do not give prompt relief, there is no contraindication to the institution of treatment with epinephrine, ephedrine or aminophylline, in fact, they can be used in conjunction with these latter drugs if it seems advisable. There are very few statistics in the literature regarding the use of the histamine antagonists in the treatment of children suffering from asthma or any other allergic disease. In one group of twenty-four children⁷ who had both single and multiple asthmatic episodes, sixteen obtained good relief from the use of benadryl. The ages of the children varied from nine months to thirteen years. Another observer⁵ reported that six children were benefited among nine treated.

Hay Fever.—Many children suffering from hay fever receive considerable symptomatic benefit from the use of benadryl or pyribenzamine. Among patients whose symptoms are severe or are complicated by much asthma, the use of these two drugs is not a substitute for a program of hyposensitization with the pollen antigen responsible for the hay fever. Benadryl and pyribenzamine are especially useful in relief of those youngsters who appear in the office for treatment for the first time during the pollen season. They are also useful to complement a program of hyposensitization which is giving the patient inadequate relief.

Pollen seasons vary in severity from year to year. Pollen counts also vary greatly from day to day. For this reason, the dose of histamine

antagonists must be varied from day to day. It is important that both the patient, or parents, and physician understand this need for adjustment of the dose to the varying needs of the patient from day to day. In thirty-six cases reported in the literature,^{5, 7} thirty-two patients obtained good relief of symptoms.

Vasomotor Rhinitis.—Patients suffering from vasomotor rhinitis frequently benefit from the use of these (antihistamine) drugs. Vasomotor rhinitis is a chronic, usually perennial, and frequently a long-standing disease. Dependence entirely on symptomatic treatment month after month with benadryl or pyribenzamine may be associated with some degree of hazard and, as noted previously herein, the patient should be seen at intervals of two months and erythrocyte and leukocyte counts should be made to ascertain the toxic effects, if any, arising from these drugs. Benadryl and pyribenzamine have their greatest field of usefulness in this disease during the period of allergic investigation and cleanup.

An additional instance in which these drugs apparently are effective was noted among a few children who perennially had plugged and running noses and who needed to undergo removal of their tonsils and adenoids, but whose congested nasal condition constantly seemed to contraindicate the procedures. Within a few days after they started to take benadryl, the nasal discharge and congestion abated, and one week to two weeks later the tonsils and adenoids were removed without incident. In each case, administration of the drug was stopped postoperatively. Its use during the first few weeks after surgery was unnecessary.

At the time of this report, one of our young patients has been taking benadryl for seventeen months. She has cerebral palsy as well as vasomotor rhinitis. Both benadryl and pyribenzamine are equally effective in controlling her nasal symptoms. The patient prefers benadryl, however, because it also controls drooling. This is probably an instance in which the dry-mouth action of benadryl is a beneficial one. This action might be useful in the control of drooling in other children, even those who do not have an underlying allergic disease.

Thorough allergic study and environmental cleanups are preferable to the long-continued use of the antihistamine drugs in vasomotor rhinitis.

Urticaria.—Those who have used the antihistamine drugs in the treatment of urticaria agree that it produces excellent therapeutic results. Prompt administration of one of these drugs usually is followed by prompt relief of symptoms. However, some of our patients who secured immediate symptomatic relief had to continue to take repeated doses every three hours for ten to twenty-one days before the urticaria cleared. More often, however, one dose is, or two doses are sufficient to produce lasting subjective and objective relief of urticaria.

urticaria It should not be concluded that either benadryl or pyribenzamine has failed unless an adequate dose has been administered

Eczema.—The results of the use of these antihistamine drugs in the treatment of eczema have been disappointing Our experience so far has shown that some of the patients experience relief of itching, but that the cutaneous lesion itself seems rarely to be abated

SUMMARY

There are available at present two drugs, benadryl and pyribenzamine, which have an antihistamine action as evidenced by laboratory data Administration of these drugs to patients has caused unpleasant side effects such as drowsiness, dryness of the mouth, vomiting and other effects in almost 30 per cent of cases Use of the drugs has had to be discontinued because of these reactions in 10 to 15 per cent of cases These drugs provide symptomatic relief only, and their use does not replace a thorough allergic investigation and the carrying out of all known precautions to avoid offending allergens The drugs have been found useful in the treatment of children suffering from asthma, hay fever, vasomotor rhinitis, urticaria and to a much less extent, eczema.

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INTOLERANCE TO COMMON DRUGS IN ASTHMA—A CLINIC*

LOUIS E. PRICKMAN AND JOHN L. MORGAN

It has long been known that individuals may exhibit bizarre and sometimes dangerous reactions after treatment with various drugs. This characteristic seems especially true of patients who have asthma, as was again forcibly brought to our attention by a series of recently hospitalized asthmatic patients. The problems involved in the management of such patients warrant re-emphasis at this time. Of the last seventeen consecutive patients who had asthma of sufficient severity to warrant hospitalization, twelve either gave a history of previous abnormal reactions to drugs or they experienced such a reaction while they were under treatment in the hospital (table 1). Seven patients reported intolerance to more than one drug.

TABLE 1

REACTIONS TO DRUGS—12 OF 17 ASTHMATIC PATIENTS SEEN CONSECUTIVELY

Drug	Reaction, type			
	Allergy	Intolerance	Overdosage	Side Effect
Aspirin	5			
Morphine sulfate		1		
Barbiturate			1	
Bromide		1		
Iodide		1		1
Chloral		1		
Iodochlorol	1			
Aminophylline				3
Benadryl				1
Pyribenzamine				1
Sulfanilamide				1
Totals	6	10	1	7

When a history of sensitivity to a specific drug is obtained from a patient who has asthma, it is not wise—indeed it is not safe—to attempt to confirm his statement either by administering the drug in question or by carrying out tests to demonstrate sensitivity to the drug. The reaction which follows the administration of even tiny quantities of a drug to which a patient is sensitive may be severe and even

* Read before the meeting of the Southern Minnesota Medical Association, Faribault, Minnesota, September 9, 1918

fatal The only safe procedure is to accept the patient's considered story when he says he is sensitive to a drug, to note the type and severity of the reactions, to stamp or otherwise indicate on all the patient's records the presence and type of drug sensitivity and to warn all personnel responsible for administering to the patient that the drug in question must not be given to that patient under any circumstances In some instances, as will be related, we observed allergic or other types of reactions to drugs during the patient's period of hospitalization In others, the only evidence obtained of reactions to drugs was the carefully checked and detailed history of previous reactions from a drug or drugs

The types of reactions that were encountered among these seventeen patients hospitalized for asthma will be considered in the next two divisions of this paper

DRUG ALLERGY

Patients who have true drug allergy respond to clinical or even subclinical doses of some specific drug to which they are sensitive by experiencing prompt and usually severe symptoms such as asthma, urticaria, vasomotor rhinitis or other allergic reactions The reaction may begin the instant the drug enters the body, usually the reaction is a matter of a few minutes, but rarely does a truly allergic reaction to drugs occur more than two hours after the administration of the drug or drugs³

The classical and by far the most frequent example of true drug allergy is that which follows the ingestion of common aspirin (acetylsalicylic acid) Five of the seventeen patients gave a history of severe allergy to aspirin, the reactions usually were asthma (status asthmaticus), but one patient said that he became unconscious and had convulsions after the ingestion of aspirin All five of the patients who had both asthma and allergy to aspirin also had nasal polyps, a triad which we have frequently noted and one which usually is indicative of a severe variety of asthma associated with a poor prognosis At least one patient in this series had both asthma and nasal polyps and was *not* sensitive to aspirin It is well known that aspirin brings relief to some patients who have asthma, and aspirin has been used in certain remedies for asthma, however, we do not administer aspirin to our asthmatic patients unless we are satisfied that the patient has recently taken aspirin without experiencing any untoward symptoms

The following two abstracts illustrate unusual types of severe allergic reactions to aspirin and a chlorine-containing radiopaque oil, and possible congenital intolerance to chloral hydrate

SOME ILLUSTRATIVE CASES

CASE 1—A Polish Jew, fifty-two years old, had undergone transurethral prostatectomy in February, 1939 This had been followed by complications requiring

Only a presumptive diagnosis may be made based on the above findings. Histologic study must be depended on to identify the lesion accurately.



Fig 61—Osteoid osteoma, left tibia (J. O., male, aged 2½ years). Roentgenogram shows an area of dense osteoid production involving the upper and medial and anterior portions of the shaft, a fusiform widening of the bone medially and anteriorly is present. The medullary cavity is slightly narrowed, in this region is a 1 cm. area of radiolucence.

TREATMENT—The nidus with its zone of surrounding bone is removed surgically.

MALIGNANT TUMORS OF THE BONES

Osteogenic Sarcoma.—The sites of most frequent occurrence are the femur, tibia and humerus, but other long bones and, more rarely, flat bones may be affected.

Pain and impaired function, while not always present, are frequent symptoms. Fever is sometimes present.

The serum alkaline phosphatase is increased in the presence of

orchectomy Asthma had developed three weeks postoperatively, becoming progressively severe. He had been free of asthma for a period of only two months (January and February, 1944) from 1939 until he was first admitted to the hospital in which we saw him in 1946. In 1941 he had spent seven months in California and Arizona, without experiencing any relief of the asthmatic state. Nasal polyps had been known to be present since 1940 and he had undergone removal of these polyps three times before we saw him. We found that the nasal polyps had recurred. Eosinophilia was present, in which eosinophils amounted to 12 per cent of the total number of leukocytes, the leukocytes numbering 7,900 per cu. mm.

The history of sensitivity to aspirin was clear-cut. In May, 1940, the patient had taken 10 grains (0.65 gm.) of aspirin for a headache, and within thirty minutes he had felt severe tightness in his throat. Very soon he had become unconscious and he had remained so for twelve hours, during which time he had had generalized convulsions.

Again in June, 1940, he had taken one tablet of a proprietary remedy (alka seltzer) which contains aspirin (acetylsalicylic acid), within two hours he had noticed "tightness" in his chest again followed by loss of consciousness and the occurrence of convulsions.

The patient had never knowingly taken aspirin or alka seltzer before May, 1940, and he had not taken any since that time. There was no other known form of drug allergy. Results of an allergic survey, in which common inhalant antigens were employed, were essentially negative. Needless to say, we did not give him acetylsalicylic acid to reproduce the attacks of unconsciousness and convulsions.

CASE 2.—The reactions to chloral hydrate and a proprietary chlorine-containing radiopaque medium (iodochlorol) experienced by the following patient were abnormal and severe. Asthma associated with a cold developed in a housewife twenty-nine years old three weeks after her second child was delivered. She had a history of "sinus trouble" since childhood. Before coming to the Clinic in May, 1946, she had been hospitalized three times for status asthmaticus, some of her more severe attacks having followed the administration of aspirin. An allergic survey showed positive reactions only to cattle hair and rabbit hair. Elevation of the bronchoscopy had been performed for her and roentgenologic studies made with radiopaque oil had been carried out. A diagnosis of cylindrical bronchiectasis had been made. No reaction had followed this procedure, in which a radiopaque oil (lipiodol) had been used.

During one phase of the patient's hospitalization the use of all medication containing barbiturates was discontinued and a total of 15 grains (2.91 g.) of chloral hydrate (Cl_2CCHO) was administered in one day. At 10:30 p. m. the patient was observed to be drowsy, she said she felt "faint." A few minutes later she did not respond to questioning. She had thirty-five respirations per minute with brief periods of apnea, the blood pressure in systole was 95 and in diastole 75 (previously it had been 100 in systole and 78 in diastole), expressed in millimeters of mercury. Within thirty minutes, during which oxygen was administered by mask, she could be aroused. No additional medication was necessary. She slept soundly and noted no ill effects the next morning. The depressing or toxic effect of chloral hydrate in this instance suggested a congenital intolerance rather than a true drug allergy.

On the fourth day after this episode with chloral hydrate, diagnostic roentgen ray studies of the bronchial tree were made with the aid of a radiopaque medium. The preparation used was iodochlorol which is said to be "prepared by combining 27 per cent of iodine and 75 per cent of chlorine with refined and purified glyceryl esters of the fatty acids of peanut oil after the free fatty acids are removed." Several days previously bronchoscopy had been performed for the

patient at which time neither bronchial stenosis nor bronchoscopic evidence of bronchiectasis had been seen. After the uneventful instillation of iodochlorol in one side, the oil was instilled into the opposite side of the thorax. Within seven minutes from the first administration of iodochlorol and after the patient had been taken to an adjoining waiting room, cyanosis, dyspnea and wheezing suddenly developed and the patient quickly became unconscious. Unconsciousness lasted about fifteen minutes, during which time the patient had generalized convulsions and a period of apnea estimated to have persisted for three minutes. Artificial respiration and the intravenous administration of 3 minims of a 1:1,000 solution of epinephrine hydrochloride and $3\frac{3}{4}$ grains (0.24 gm) of aminophylline were needed before consciousness returned and the asthma was controlled. There were no similar episodes.

The suddenness and severity of this latter reaction, which was associated with asthma and bronchospasm as well as with unconsciousness and convulsions, seems classified as a true drug allergy to iodochlorol or one of its constituents.

INTOLERANCE TO DRUGS

Several other types of reactions to drugs were encountered among these patients hospitalized for asthma. These reactions varied from so-called side-effects to toxicity arising from usually innocuous doses of common drugs, or to reactions from possible overdosage of a drug. In the treatment of patients who have asthma and other allergic conditions, the physician should be constantly on the alert to observe any change in the patient or symptoms that could indicate early intolerance to a drug.

Some of the mild side-effects of drugs encountered in the treatment of asthma included nausea and occasional vomiting in several patients who received intravenously, 200 cc of a 20 per cent solution of glucose containing $3\frac{3}{4}$ grains (0.24 gm) of aminophylline. In no instance were these symptoms of sufficient consequence to compel discontinuance of the use of the drug. Rectal administration of aminophylline to these patients usually was well tolerated, but occasionally the agent thus administered was much less effective in relieving severe asthma than it was when it was administered intravenously.

In two instances drowsiness that was annoying was noted after the administration of benadryl and pyribenzamine. This symptom disappeared when administration of the drugs was discontinued.

One patient said that sulfanilamide had caused her to vomit, but she was able to take sulfadiazine without distress while she was under our care.

A curious but apparently authentic side effect experienced by one patient was anorexia which occurred each time iodides were administered for asthma. The anorexia disappeared when the use of iodides was discontinued.

Morphine sulfate and codeine are definitely contraindicated in the treatment of asthma because they contribute to retention of bronchial secretions by means of the depressing effect they exert on the respira-

tory center. The drugs are not used on our service, but morphine had been used previously in the treatment of several of our patients and in four patients had caused such side effects as nausea and vomiting and in one instance prolonged unconsciousness, possibly the effect of overdosage. It has also been observed that no matter how effective morphine may be in quieting the patient and relieving his apprehension, the asthma itself is not benefited and the wheezing continues unabated. One of us (Prickman) has observed asthmatic wheezing and dyspnea after overdosage of morphine to the extent that respirations were reduced to five a minute and artificial respiration in the Drinker respirator was required. Even though extreme narcosis and suppression of breathing occurred, asthmatic respiration continued unabated in this patient and was still present and still severe when consciousness returned. Unger wrote that morphine is the chief cause of death in asthma. Without question, it is a dangerous drug to use in asthma and one which courts catastrophe. In spite of repeated warnings of this nature, morphine still is frequently prescribed for asthma.

Iodides are among the most effective expectorants and are almost routinely used in the treatment of asthma. Many patients exhibit a limited tolerance of iodides, a papular rash or congestion of the salivary glands develops when their tolerance is exceeded. Tolerance may be limited to only one or two 10 grain (0.65 gm.) doses of potassium iodide, more often patients can take iodides several days before signs of intolerance appear.

A female patient whom we previously had hospitalized for treatment of asthma was readmitted because of extensive fungating moist lesions of the face and arms (fig 157, *a* and *b*). Nodules were present, with necrotic depressed centers on the right side of the face involving the eyelids and nose. Bromide intoxication was suspected because she had been taking a bromide-containing mixture several times daily for a period of four weeks. The concentration of bromide in the blood was found to be 7 mg. per 100 cc. The lesions regressed promptly but slowly when bromide medication was discontinued, a week later bromide was not found in the blood. This patient had severe asthma on admission and during the first days in the hospital. The intravenous administration of aminophylline and the repeated hypodermic injection of a 1:1,000 solution of epinephrine hydrochloride in 5 min. doses satisfactorily controlled the asthma.

Many remedies for asthma and hay fever contain barbiturates, and because anxiety is associated with asthma it seems common practice to administer additional barbiturates to asthmatic patients as sedative and soporific agents. If the physician and patient are not alert therefore, the patient may be taking an overdose, or toxic dose of this useful group of drugs. Some patients also are rather sensitive to, or intolerant of even small doses of the barbitol compounds and



Fig 157—Lesions secondary to sensitivity to bromides *a*, face of patient, *b*, left arm of same patient, showing fungating lesions caused by sensitivity Both photographs were made on the same day

they react abnormally. The physician who is treating asthma must, therefore, have a low threshold of suspicion for barbitol intoxication in its different forms

AN ILLUSTRATIVE CASE

As an example, a sixty-two year old farmer who had severe asthma of more than three months' duration was making unsatisfactory progress in the hospital. The asthma was not too severe after a few days, but he remained anxious and depressed. Because of this he was given $\frac{1}{2}$ grain (0.032 gm.) of phenobarbital three times daily for two days, in addition to other medication. Among the latter were a phenobarbital-containing proprietary agent for oral use amounting to $\frac{1}{3}$ grain (0.021 gm.) daily, and a rectal proprietary agent containing, in addition to $5\frac{1}{2}$ grains (0.33 gm.) of aminophylline, $1\frac{1}{2}$ grains (0.1 gm.) of pentobarbital sodium. At the end of this time he was disoriented, negativistic and restless. The administration of phenobarbital was discontinued, and 3 grains (0.2 gm.) of sodium amytal was given at bedtime during the next few days, with no change in the patient's symptoms. The use of all barbiturates was then discontinued. Within twenty-four hours thereafter the patient became co-operative, alert and well oriented. The asthma, meantime had been controlled.

COMMENT

The entire subject of sensitivity to drugs is large and involved, and in the present paper it is merely touched upon as it occurred in seven teen consecutive patients who had asthma. Still other important examples of hypersensitivity to drugs might be selected from a more inclusive group of cases. One type or degree of hypersensitivity to drugs not encountered in our limited series should be re-emphasized at this time because of its serious implications in connection with drug therapy in asthma, and also because it illustrates the danger of continued administration of a drug after signs of intolerance to that drug have become apparent.

In a series of reports since 1942, Rich^{4, 5} has shown that the lesions of periarteritis nodosa may be encountered in patients dying after severe serum disease had developed, or after they had shown signs of intolerance to such drugs as sulfonamides and iodides.⁶ In another instance biopsy of muscle from a patient who subsequently recovered disclosed lesions of periarteritis nodosa, after the patient had received antiserum for pneumonia followed by serum sickness and symptoms suggesting periarteritis nodosa.

It would be anticipated from these observations of Rich and others that with the increased use of sulfonamides and other chemical substances in recent years there would result increased evidence of necropsy of periarteritis nodosa, and this apparently has been true.

Since sulfonamides frequently are administered for certain complications of asthma, such as acute respiratory infections, sinusitis, pneumonia and bronchitis, the physician should always bear in mind that sensitivity to sulfonamides can occur so that administration of the

drug must be discontinued very promptly at the earliest signs of intolerance

Considering the frequency with which iodine is administered to patients who have asthma, bronchitis, emphysema and goiter and the relative frequency with which limited tolerance for iodides occurs, it is to be wondered that allergic sensitivity to iodides does not occur more frequently than it has been reported. Rich has reported such a case of sensitivity to iodides, however, and was again able to find typical lesions of periarteritis nodosa at necropsy. The administration of iodides had been continued after signs of intolerance appeared.

The mechanism whereby a nonantigenic chemical may act as an antigen and induce hypersensitivity similar to that caused by many proteins has been elucidated by Landsteiner, who showed that chemicals may be combined with a protein—for example plasma—and then act as a new specific antigen. Hypersensitivity may occur from any drug or chemical, and in practice few if any drugs have been used extensively without there being reported in due time hypersensitivity to that drug.

CONCLUSIONS

Drug allergy and various types of intolerance to drugs are encountered rather frequently in the treatment of patients who have asthma. Each asthmatic patient must be observed carefully for early evidence of such intolerance, and patients who have asthma must be carefully questioned about previous reactions to drugs of any and all types, and use of the drug or drugs responsible must be meticulously avoided.

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EXFOLIATIVE DERMATITIS. CLASSIFICATION, DIAGNOSIS AND TREATMENT

ROBERT R KIERLAND

EXFOLIATIVE dermatitis is an accepted diagnosis of medicine. Yet for those who deal with and treat cutaneous disease it is better that exfoliative dermatitis be considered as a symptom complex of the skin which may be caused by diverse and unrelated factors. Exfoliative dermatitis may represent a reflection on the skin of serious systemic disease, may be an extension of a pre-existing cutaneous disease or may arise from purely local conditions. In certain instances a satisfactory etiologic factor cannot be obtained. It is highly important that an etiologic diagnosis be made if at all possible.

Exfoliative dermatitis may be defined as a generalized or universal, superficial or deep, diffuse, inflammatory exfoliation of the skin, frequently associated with paroxysms of pruritus, secondary crusting, exudation or fissuring and due to factors known or unknown. All gradations of severity may be seen, varying from simple mild erythema and scaling to an intense inflammatory reaction of the skin accompanied by severe systemic manifestations of dehydration, toxemia and hypoproteinemia.

Many classifications of the types and causes of exfoliative dermatitis have been given, no one of which is completely satisfactory. The one given in the next section has the advantage of simplicity and lends itself to the more important problem of proper diagnosis and treatment.

CLASSIFICATION OF EXFOLIATIVE DERMATITIS

1. Caused by extrinsic agents
 - A. Sensitivity to external agents, usually local medications or contact agents as
Ragweed, dyes, mercury, tar, sulfonamides
 - B. Sensitivity to internal agents, usually medications, such as
Gold, arsenic, barbiturates, quinine, sulfonamides, atabrine, penicillin
2. Extension of other cutaneous diseases or secondary to them or both
 - Psoriasis
 - Pityriasis rubra pilaris
 - Seborrheic dermatitis
 - Pityriasis rosea
 - Lichen planus
 - Ichthyosiform erythroderma
 - Pemphigus foliaceus
3. Secondary to systemic disease
 - Lymphoblastomas
 - Atopic dermatitis
4. Idiopathic types
 - Wilson-Brocq
 - Pityriasis rubra of Hebra
 - Rutter, Lennar and Savill types in children

Certain of the diseases mentioned in group 2 of the classification, such as psoriasis, pityriasis rubra pilaris and others may belong more appropriately to group 3, yet the extracutaneous signs and symptoms of these conditions are meager and for that reason these diseases are classified as they are. Later, perhaps, as more knowledge of many of these conditions is gained, they will be grouped differently. Furthermore, the categories mentioned earlier in this section may merge into one another, for instance, psoriasis may be treated too intensively with a chrysarobin or mercury preparation, with resultant generalization of sensitization or contact dermatitis. Similarly a patient who has atopic dermatitis may receive ultraviolet irradiation to which he is hypersensitive and the condition thus becomes generalized or universal.

SYMPTOMATOLOGY

In discussing the symptomatology of exfoliative dermatitis, the subject will be considered broadly since a complete presentation of each condition that may eventuate into exfoliative dermatitis would be beyond the scope of this paper. In the section on diagnosis, the essential diagnostic findings will be given.

The subjective symptoms of a patient who has exfoliative dermatitis are varied. Frequently, the patient has no subjective complaints at any time, as in some cases of exfoliative psoriasis or pityriasis rubra pilaris. More often, however, pruritus is a prominent symptom in the majority of cases in which exfoliation occurs from any cause. Pruritus occurs in paroxysms of varying intensity, usually at night. Burning and other paresthesias may be prominent. A sensation of chilliness is frequently noted. This is due to a more rapid loss of heat from the red and inflamed skin than occurs in normal persons. The patient may also complain of various extracutaneous symptoms, as diarrhea, headache, malaise, lassitude and others, depending on the cause of the condition and the severity of the process.

The objective systemic findings of examination depend almost entirely on the cause of the patient's exfoliative cutaneous disease. The reactivity of the skin varies markedly. All gradations of cutaneous involvement are seen from the acute scarlatiniform erythema of dermatitis medicamentosa due to a barbiturate or quinine to the dull erythematous, heavily lichenified skin of a patient who has chronic neurodermatitis.

In cases of exfoliative dermatitis due to a sensitivity to medications used locally or taken internally, the process is usually an acute one with an acutely developing, brilliant erythema. The full development of the dermatitis is reached in a few days to two weeks, after which the redness becomes duller, exfoliation begins and the dermatitis gradually clears. Exudation of serum from the acutely inflamed skin

may appear at the height of the process, being usually most prominent on the lower extremities, face, ears and in the case of a local reaction at the site of the application of the medication

The dermatosis assumes a chronic character when the exfoliative reaction is a part of an extension of specific cutaneous disease or when it is secondary to systemic disease. In this instance, the skin has a dull red hue, is frequently lichenified and presents varying degrees of scaling. The type of scale present is usually not diagnostic but is sometimes suggestive, as in cases of pemphigus foliaceus.

In addition to scaling, erythema and lichenification of the skin, certain other changes may occur in special sites. The hair may be temporarily lost. The nails frequently become thickened, furrowed and soft, then lose their attachments and are gradually shed. Infiltration of the skin about the eyes may result in ectropion. The palms and soles may remain normal but are frequently thickened, fissured and painful. Generalized adenopathy is usually present.

In cases of chronic types of universal exfoliation, exudation of serum with secondary crusting may also be present and sometimes involves a large part of the cutaneous surface. With the loss of protein either by shedding of the scales or by exudation of serum, a state of hypoproteinemia frequently develops. The basal metabolic rate is usually elevated, owing to the loss of heat from the cutaneous surface.

DIAGNOSIS

It should again be emphasized that exfoliative dermatitis is a symptom and not a diagnosis. The proper diagnosis of the type of exfoliative dermatitis encountered rests frequently on concomitant evidence rather than on the findings on the skin itself.

A history of the site of origin and type of the original eruption and its subsequent progression is essential. The reaction to medications applied to the eruption or taken internally should be ascertained. The story of associated disease should be elicited as, for example, asthma and hay fever in association with atopic dermatitis. An attempt should be made to find other associated factors such as the following: family history of cutaneous disease, the influence of diet and emotional tension on the eruption, the subjective symptoms—that is, whether itching or burning—and general symptoms such as fever, gastrointestinal disturbance, headache and malaise.

The skin must be thoroughly examined. While the degree of lichenification and erythema and the type of scale are not diagnostic as a rule, frequently one may find the primary lesion of the eruption or other evidence of the basic disease on the skin or its appendages.

Removal of a specimen of skin for histopathologic examination is important and should be done in all obscure cases. The site from which the specimen is removed for biopsy should be chosen with care.

if possible, the primary lesion should be removed and areas with secondary changes should be avoided. Occasionally, a biopsy of a lymph node is advisable but this should not be done unless the diagnosis cannot be made by other means. The objection is that many of the operative sites become severely infected.

The laboratory also aids in the proper diagnosis of patients with exfoliative dermatitis. On all patients who have a chronic form of the disease, urinalysis, determination of the hemoglobin, the number of erythrocytes and leukocytes, differential count of the leukocytes and morphologic examination of the cells should be done. Roentgenologic examination of the thorax, the sedimentation rate and the protein value of the serum are other important examinations. Other examinations should be done when indicated.

With the foregoing discussion as a preliminary, the diagnostic features of the conditions in each category may now be considered briefly.

Exfoliative dermatitis due to the local application or internal administration of medications or contact agents usually has an acute, rapid course. The eruption itself begins as a bright morbilliform or scarlatiniform erythema, which rapidly becomes universal in distribution. The eruptions due to atropine, barbiturates and quinine usually fade out in a few days to a week. However, those due to repeated contact with ragweed or other agents may progress to the chronic form. Of diagnostic importance are the history of medication or contact agent and the site of major involvement and progression. Dermatitis from contact agents reaches its greatest extent on the exposed sites of the skin. The genitals and eyelids are frequently involved in any type of contact dermatitis.

The exfoliative eruptions from gold and arsenic begin acutely but persist for a long period. Prodromal symptoms may be generalized pruritus and transient erythemas. Chemical examination of the urine, hair and nails reveals the drug to be present in excess amounts.

Specific cutaneous diseases which progress to exfoliative dermatitis are usually found to retain certain of their diagnostic features. The modification of the eruption from previous treatment is important to remember. The preceding history in all of these cases is highly important.

Psoriasis may be recognized frequently by the presence on the scalp, elbows and knees of the mica-like, scaly plaques even in the presence of universal exfoliation. The nails may show the characteristic involvement of a thumb-like type of pitting and lateral onycholysis. The pathologic examination of a specimen of skin is helpful, as psoriasis presents a rather characteristic histopathologic picture which is retained in exfoliative dermatitis of psoriatic origin. There are no distinctive laboratory findings.

The features of universal pityriasis rubra pilaris are found in the

osteogenic sarcoma in some instances and is a desirable corroborative test.

1 *Osteolytic type* Roentgenographically there is an irregular area of destruction without enlargement of the shaft of the bone. Periosteal reaction may be present over the involved cortex. This tumor resembles other bone tumors and, at times, osteomyelitis. Biopsy may be required for differentiation.

2 *Osteoblastic type* Sclerosing osteogenic sarcomas are unusual in children. Roentgenographically the findings are (a) metaphyseal location of the tumor, generally without epiphyseal involvement, (b)



Fig. 62—Fibrosarcoma (J. B., male, aged 2 months). The swelling of the right forearm was noticed shortly after birth. Biopsy showed fibrosarcoma.

dense osteoid formation with loss of normal osseous markings, (c) periosteal elevation with "lipping" and separation of the periosteal outline, and (d) radiating "sun-ray" appearance of spicules of bone. 3 *Chondrosarcoma* This tumor occurs most commonly at the lower end of the femur, the upper end of the tibia and the upper end of the humerus. Roentgenographically it is identified by (a) the site, (b) a soft shadow near the cortex, (c) periosteal elevation, and (d) absence of reaction in the bone itself.

TREATMENT—Radiation therapy followed by resection or amputation is the accepted treatment.

Endothelioma (Ewing's Tumor)—Endothelial myeloma is char-

horny follicular papules, each pierced by a stub of hair, on the dorsum of the fingers and in the waxy keratoderma of the palms and soles, the hue of which has been likened to that of carnauba wax. The salmon-red hue of the expressionless face of the patient is often distinctive. The disease may occur at any age but the onset is most frequent during childhood. The pathologic findings of a biopsy are significant. The results of the common laboratory examinations are essentially normal, though if a vitamin A tolerance test be done there may be depressed values and a flattening of the curve.

If seborrheic dermatitis becomes universal, the history of onset and the primary sites involved usually lead to the correct diagnosis. The eruption is most prominent in the so-called seborrheic areas—face, scalp, presternal areas, the upper part of the back and the body folds. The scaling tends to be greasy. While the histopathologic findings may not be distinctive, other conditions may be ruled out by means of a biopsy. The results of urinalysis and other procedures are usually normal.

Pityriasis rosea and lichen planus rarely become sufficiently generalized to be considered within the scope of exfoliative dermatitis. Even when they do, however, the story of onset and the sites of the original eruption are sufficiently clear-cut usually to permit a diagnosis. Histologic diagnosis of lichen planus can be made. The findings are not well defined in pityriasis rosea while the laboratory is of little value in the diagnosis of either condition.

Pemphigus foliaceus may begin with the ordinary type of bullous eruption as seen in pemphigus vulgaris, only to develop the exfoliative reaction later in its course, or it may exist in the form of an exfoliative dermatitis at the outset. The patient is toxic and frequently has a low fever. The scales are easily detached, leaving a moist surface of inflamed skin. The hair and nails are frequently lost. Ectropion is frequent and is due to the inflammatory infiltrate about the face. The eruption is more moist than in the other types of exfoliative dermatitis and, during its course, bullae are often present. Nikolsky's sign (stripping of the skin) is usually present. Also, in contrast to the other types of exfoliative dermatitis, there is the frequent involvement of the mucous membranes, which participate in the exfoliative process. Death usually results from intercurrent infection or from cachexia. The findings from the laboratory show a varying degree of anemia, occasionally eosinophilia, and increased sedimentation rate and hyperproteinemia. The histopathologic findings more than anything tend to rule out other conditions, although edema is a prominent feature and that superficial layers of the epidermis may be lost.

Ichthyosiform erythroderma is a rare congenital disease which, as its name implies, consists of ichthyosis with the added feature of erythema. Occasionally, bullae are found, which disappear without

sequelae The sites of major involvement are the flexural surfaces in contrast to the usual forms of ichthyosis The disorder is usually benign and the erythematous feature may disappear in adult life There are few if any subjective symptoms except decreased sweating The laboratory findings are not remarkable while the histologic features are those of ichthyosis with a slight inflammatory reaction

Atopic dermatitis (neurodermatitis) frequently becomes universal in extent It is here included in the group of exfoliative dermatoses secondary to systemic disease because of its frequent association with an allergic background The patient or his relatives usually give a history of allergy, present or previous, such as asthma, urticaria, hay fever or eczema The patient may give a history of infantile eczema which disappeared, only to reappear later in the form of a pruritic, dry, scaly eruption limited to the face, neck and the antecubital and popliteal surfaces From here, the eruption may generalize or it may originate as an exfoliative dermatitis The explosive mechanism may be an emotional shock or a dietary indiscretion or it may remain unknown A characteristic finding in universal neurodermatitis is the "tache blanche" or white dermographia This is manifested by the appearance of a white linear streak on stroking the skin rather than the red streak evoked in normal people and in other conditions The dermatosis is usually dry but there may be repeated episodes of exudation, often without explanation The histologic examination of a specimen for biopsy is sometimes distinctive Eosinophilia is usually found on the differential count of the leukocytes of the peripheral blood

The lymphoblastomas are the largest group of systemic diseases in which exfoliative dermatitis is seen It is here that biopsies of the skin and a lymph node and the morphologic examination of the cells of the peripheral blood reach their greatest diagnostic importance in exfoliative dermatitis The lymphoblastomas include the various leukemias, lymphosarcoma, including Hodgkin's disease, mycosis fungoides and a few more rare conditions The term "malignant erythroderma" has been applied to exfoliative dermatitis of this type While the skin may be tremendously thickened and infiltrated, there is frequently but little scaling Frequently, in addition to the universal exfoliation, there are infiltrated nodules and tumors scattered about the skin It is preferable that the specimen for biopsy be taken from an infiltrated lesion

Mycosis fungoides is primarily a cutaneous disease but the patient may show evidence of other of the group of lymphoblastoma in the evolution of the disease The cutaneous lesions of the other lymphoblastomas are usually secondary to metastasis but may rarely originate in the skin The different conditions comprising the group of lymphoblastomas are so closely allied that in the same patient multiple

diagnoses may be entertained as the result of different pathological findings in the blood, lymph node and skin. Exfoliative dermatitis accounts for about a third of all types of cutaneous lymphoblastoma. It is seen especially in the later decades of life, in which 30 to 50 per cent of all cases of exfoliative dermatitis are of lymphoblastic origin. While all patients who have this condition have a fatal outcome, the patient may survive for many years.

In the older literature, two types of exfoliative dermatitis were described which have carried to the present the names of the Wilson-Brocq type and pityriasis rubra of Hebra. If actually these are distinct entities, they must be extremely rare. It would seem that, as knowledge of the causes of exfoliative dermatitis increased, patients who were formerly classified in these two types were placed in other categories. Certainly the Wilson-Brocq type when fully developed cannot be distinguished on clinical grounds from exfoliative reactions of other diseases. The older descriptions of pityriasis rubra of Hebra seem to fit most closely the exfoliative dermatitis of lymphoblastoma. It is evident though that the cause of exfoliative dermatitis in many cases is unrecognized or, in the present state of our knowledge, unknown.

In infants and children, types of exfoliative dermatitis were long ago described by Rutter, Leiner and Savill. These are rare conditions if such types do exist. The first, Rutter's disease, appears to be a variant of streptococcal impetigo in infants.

COMPLICATIONS

The complications of exfoliative dermatitis may be mild or severe. The most common complication of the skin is secondary infection with pyogenic organisms. This usually remains localized on the skin but may invade the lymph channels to produce lymphangitis and lymphadenitis or may cause septicemia, pyemia and metastatic abscesses by invasion of the blood. *Cornebacterium diptheriae* may also be a secondary invader and may remain unrecognized until the development of peripheral neuritis or myocarditis. Waterhouse-Friedrichsen syndrome is rare but does occur, most often among children.

Pneumonia is perhaps the most common of the serious systemic complications. Hypoproteinemias is a common occurrence and serves as a warning of future inanition. Indications of hepatitis and nephritis may appear as a toxic reaction. In patients with a long-protracted course of exfoliative dermatitis, a higher incidence of tuberculosis than in normal persons is recorded.

If death occurs, it may be due to the disease itself, as in lymphoblastoma, to intercurrent infection, as pneumonia, or to inanition and exhaustion.

TREATMENT

Treatment of exfoliative dermatitis is a difficult problem and frequently unsatisfactory. Fortunately, however, attempts can be made to relieve the patient's discomfort while measures are being taken to make the proper diagnosis.

Local treatment to the skin is dependent on the acuity or chronicity of the exfoliative process and on the amount of exudation. In acute, exudative reactions, treatment must be soothing and gentle, preferably in the form of baths, wet dressings and soothing lotions. Soothing baths may be made according to the following procedures. A starch and soda bath is prepared by making a cold water paste of 1 cup (240 c.c.) of cornstarch and $\frac{1}{4}$ cup (60 c.c.) of baking soda. This is then placed into about one-half tub of warm water. The patient bathes in this for twenty to thirty minutes daily or less often if the skin becomes too dry. A colloid or oatmeal bath is prepared as follows. Boil 2 cups (480 c.c.) of bulk oatmeal in 1 quart (1 liter) of water for thirty to forty-five minutes in a double boiler. Allow to cool for fifteen minutes, then add $\frac{1}{2}$ cup (120 c.c.) of baking soda. Pour the entire mixture into a gauze bag and tie shut. Place in a bathtub one-half to three-fourths full of water at about 90° to 96° F. The patient may stay in the tub one-half to two hours expressing the oatmeal mash through the gauze and applying it over the body. The mash is washed off thoroughly before the patient leaves the tub. Drying should be done by patting and blotting rather than by rubbing.

Many forms of wet dressing are used and may be partially listed as follows: isotonic saline solution 0.9 per cent, boric acid 2 to 4 per cent, aluminum subacetate (modified Burow's solution) 0.5 per cent, alibour water 0.5 per cent, potassium permanganate in a dilution of 1:8,000 to 1:16,000 and silver nitrate 1:500 to 1:1,000. The dressings should be changed frequently, every two to three hours, so that the strength of the solution is not increased by evaporation of the water. The dressings should not be covered by impermeable material, as this, if done, leads to overheating and undue maceration. No more than a third of the body should be covered with a wet dressing at any one time because of the danger of chilling and subsequent pneumonia.

As the acuity of the process subsides, "shake lotions," as calamine lotion, may be substituted gradually for the wet dressings. If the area to which the lotion is to be applied is large, other medications, such as phenol, should not be added to the lotion because of the danger of absorption. If the lotion proves too drying, a mild, nonirritant ointment or oil may be applied over the lotion.

The use of ointments is indicated when the process has reached a subacute or chronic phase of activity. They should be applied cautiously and a "trial" should be given first. This consists of applying the ointment to a small area of skin for at least twenty-four hours before

using it generally over the body. In this manner, many of the serious local, untoward reactions from treatment may be avoided. If the "trial" is well tolerated, the ointment may then be spread gradually over the skin.

In patients exhibiting chronic lichenified eruptions, stimulating ointments containing tar and salicylic acid may be tried cautiously at the outset of treatment, using the "trial" method as indicated in the preceding paragraph. If there is any doubt, however, the soothing types of ointments should be used first. Brief, gradually increasing exposure to ultraviolet radiation is of definite value in chronic forms of exfoliative dermatitis, especially when the irradiation is given through a thin film of crude coal tar.

It is difficult to suggest on paper what is the best preparation for use on any given patient, and for this reason, the following general suggestions of therapy are given. The choice and vehicle of a medication are determined by the morphologic characteristics of the eruption. If in doubt, start treatment with the most soothing measures, gradually working up from wet dressings to lotions, from lotions to mild ointments and from soothing ointments to stimulating ones. There is always a possibility that a medication may harm rather than relieve and, for this reason, "trials" of new remedies should be used. Avoid changing to a new treatment as long as the eruption is improving under the old one.

Patients who have exfoliative dermatitis need treatment internally as well as externally. It is important that a highly nutritious, high-protein diet be provided for those patients who exude much serum and for those who have depressed values of protein. The diet may be supplemented, if necessary, by the oral administration of amino acids or by transfusion of whole blood or of plasma. In addition to supplying proteins, repeated small infusions of whole blood seem to exert a marked tonic effect on many patients. Elimination diets may be of some help in the management of patients who have universal atopic dermatitis, although this is unusual. Supplemental administration of vitamins has been recommended and seems of some value in isolated instances.

The antihistamine preparations, benadryl and pyribenzamine, do of some help in relieving paroxysms of pruritus but seem of little value against the eruption itself. Autologous serum therapy—that is, the intramuscular administration of 5 to 10 cc of the patient's own blood two to three times weekly—is of value and seems to act in the manner of a foreign protein. Other medications, as the intravenous use of sodium or calcium thiosulfate, may be used but the detoxicating effect of the thiosulfates has been largely disproved.

In a few types of exfoliative dermatitis, other therapeutic measures are available. Dimercaprol (BAL, British antilewisite) should be

to all patients whose dermatitis is due to arsenic. While exfoliative reactions from bismuth, mercury and gold are more uncommon, BAL is of value in mercurial poisoning and may well help those reactions due to bismuth and gold. Roentgen therapy is of much palliative value in the treatment of the cutaneous exfoliation of lymphoblastoma but must be given by those trained in its use. Roentgen therapy may be used in other types of exfoliative dermatitis as well. The results from the use of nitrogen mustard and urethane in the treatment of the cutaneous reactions of lymphoblastoma are indeterminate as yet. Arsenic is of value in the treatment of pemphigus foliaceus.

CONCLUSIONS

Exfoliative dermatitis is a cutaneous reaction caused by many unrelated factors and for that reason is only an unsatisfactory morphologic diagnosis. This reaction should be considered as a symptom rather than a diagnosis. The various etiologic factors are considered and the salient diagnostic and therapeutic measures are discussed.

ATOMIC ENERGY IN MEDICAL PRACTICE*

FRANK H. KRUSEN

"ATOMIC POWER"

Before recorded history began
Prometheus, symbol of Science, brought us fire,
The altar and the hearth were our desire,
On these were built the faith and hope of man
Then wood and stone and bronze and steel and steam
In turn became the servants of our will,
Knowledge we got and with it thought to fill
Each need and want, to realize each dream
Again Prometheus brings a magic gift,
Which scarce we know if we should ban or bless
The boldest hesitate, the fearful cower,
Before this weapon, deadly, sure and swift
Amazed we stand, appalled at our success,
For who are we to wield this cosmic power?

—THOMSON KING

WHenever I have attended a medical meeting at which the uses and dangers of atomic energy were discussed, the medical audience has been extremely solemn and attentive. Obviously all physicians are aware of the fearful potentialities of atomic energy and wish to learn as much as possible concerning it.

THE GOVERNMENTAL PROGRAM IN DEVELOPMENT OF CONSTRUCTIVE USES OF ATOMIC ENERGY

It is perhaps well to know something about the government's plan for development of research in medical applications of atomic energy. Actually, although much has been accomplished, no final plans have been announced as yet. The governmental developments started with the work of Section S-1 on Atomic Energy of the Office of Scientific Research and Development and continued with activities of the Manhattan Engineering District Investigating Group. Then the Secretary of War's Interim Committee on Atomic Energy was established.

Working with this Interim Committee, Manhattan Engineering District Group developed excellent plans for making radio-isotopes available for medical research. This led to publication of an announcement from headquarters of the Manhattan project on "Availability of

* Revised and enlarged from a paper on "The general medical aspects of atomic energy." Read at a meeting of the American Pharmaceutical Manufacturers Association, New York City, New York, December 10, 1940.

radioactive isotopes²³ A committee of scientists has been attempting to develop a suitable interim mechanism for allocation and distribution of radio-isotopes

Supplementing these developments, the office of Mr Bernard M Baruch, formerly United States Representative to the United Nations Atomic Energy Commission, with Dr Richard C Tolman as scientific adviser, prepared a number of extremely important reports, including volume 1 on general scientific information, volume 3, a bibliography and check list, and volume 5 on medical uses of atomic energy The final decisions with regard to the government's plan for development of research on medical aspects of atomic energy will rest with the recently appointed five man national Atomic Energy Commission under the chairmanship of Mr David E Lihenthal

FUNDAMENTAL CONSIDERATIONS WITH REGARD TO MEDICAL USES OF ATOMIC ENERGY

Application of physics in the practice of medicine began fifty years ago with Roentgen's discovery of roentgen rays Since then exploration of atomic and molecular structure has been a major concern of most physicists²⁰ Knowledge of this subject advanced with John Dalton's assumption that chemical compounds are composed of molecules which, in turn, are made up of atoms

A simple description of some of the developments in knowledge of atomic energy contributes to the understanding of the general medical aspects These have been well described by Bacher and Feynman. Up until the time of the recent studies on atomic energy, scientists had been able, for the most part, simply to regroup atoms into new patterns Now nuclear physicists have discovered ways to transform atoms from one kind to another This new ability to transmute elements rather than just to rearrange them permits control over an entirely new group of natural phenomena

Each atom consists of an electron cloud in the center of which is a heavy nucleus Approximately 600 varieties of atoms are known Many have the same kind of electron cloud but possess a different kind of nucleus Two atoms that have different cores but similar electron clouds are called "isotopes" Different isotopes of a single element usually are distinguished by giving each a number This number represents the weight of the nucleus Thus, two hydrogen isotopes are known as H^1 and H^2 There are two principal isotopes of natural uranium, U^{233} and U^{235}

What nuclear physicists have discovered is a way to change the nucleus of the atom Rutherford was the first scientist to succeed in changing the nucleus of the atom He accomplished this feat in 1919 by bombarding nitrogen with alpha particles thus changing it into oxygen and hydrogen Later with invention of the cyclotron and other

devices for producing streams of hydrogen, deuterium or helium nuclei, which have kinetic energies of several million electron volts, many other artificial transmutations of elements have been accomplished by conversion of their nuclei. The new nucleus, however, may not be stable. When the nucleus changes, it may emit gamma rays. An isotope which is capable of changing from one kind to another is called a radio-isotope. Since radioactivity can be detected easily with modern instruments, radio-isotopes can be located readily among stable atoms. This ability to detect the presence of radioactive isotopes is of tremendous value in the solution of many biologic and chemical problems. Radio-isotopes can be used in medicine and in scientific research as tracer elements.

In 1932, Chadwick proved that particles penetrating atoms had about the same mass as protons but possessed no electric charge. Therefore he called them neutrons. It is now the generally accepted opinion that all atomic nuclei are built up of neutrons and protons.

By 1934, Fermi had bombarded a large number of chemical elements with neutrons. Because the neutron has no electrical charge, it is not repelled by the atomic nucleus but enters it and thus a new nucleus is formed which usually is radioactive.

The fission phenomenon was discovered in 1939. When uranium was bombarded with neutrons, it was found that one of the reaction products was a radioactive form of barium. Meitner concluded that the barium must have been produced by fission, or splitting, of the uranium atom into two nearly equal parts.

Soon it was realized that if it were possible to cause all the atoms in 1 pound (0.5 kg.) of uranium to undergo fission, approximately 10,000,000 kilowatt-hours of energy would be liberated. Likewise, when it was discovered that two or three neutrons are ejected from the atom during the process of fission, it became apparent that these neutrons might in turn produce fission in other atoms and so on until a self-perpetuating chain reaction occurred which would release enormous amounts of energy.

Then came the work with fission of U^{235} (plutonium) which produced a tremendous explosive release of nuclear energy and the atomic bomb was born.

Nichols and Ruhoff have said that some of the most important by-products of development of the atomic bomb are the host of new tools that are now available for basic research in many fields including medicine, chemistry and physics. New radioactive materials can be produced synthetically in a pile. Also, new radioactive fission materials, new chemical and physical processes and new mathematical techniques have been produced. In the sum total of their applications these new technical and engineering methods may be of greater value than the power potentialities of atomic energy.

Cohn said that most of the radioactive species produced in a pile can also be made in a cyclotron. A few species occur as the result of fission, however, which cannot be made conveniently otherwise. The combined use of the pile and the cyclotron has brought the present list of radio-isotopes to about 450. The important contribution of the pile is that it can make certain radio-isotopes available in tremendous quantities.

By virtue of their radioactivity, radio-isotopes can be detected at a distance. Therefore, samples need not be purified to the extent necessary for ordinary physical or chemical analyses. Furthermore, the fact that each radio-isotope has its own specific and unique type of radiation permits exact identification.

Of particular significance in medicine is the fact that radiation from radio-iodine extends outside of the human body and its approximate location can be detected by placing instruments on the surface of the body. For example, in studying the effect of radio-iodine on the thyroid gland, the rate at which it enters and leaves the gland can be followed continuously. Such studies were impossible before manufacture of radio-iodine. Once proper information was available, a method of utilizing larger amounts of radio-iodine in treatment for hyperthyroidism was developed.

It has been stressed by Allison and by Cohn that there are tremendous possibilities of utilization of radio-carbon because among the many atomic species which make up living matter carbon occupies a unique position owing to the enormous number of compounds it can form. Cohn expressed the opinion that it is possible that discoveries made in researches with the carbon isotope C^{14} may be as important and far-reaching as the discovery of fission itself. However, because of its long life, use of C^{14} therapeutically may be extremely dangerous.

ATOMIC ENERGY AS A SOURCE OF POWER

Before turning to general medical applications of atomic energy, I would like to consider the point which has been made with regard to industrial power. Industrial scientists are in general agreement concerning the fact that a tested method of extracting energy from atoms for production of industrial power is not known nor is one likely to be known for several years. Known supplies of uranium and thorium are limited. U^{235} , which must be extracted from U^{238} (uranium in its natural state), is costly. Because it does not produce high enough temperatures for power, U^{238} must be enriched by U^{235} .

One pound (0.5 kg) of U^{235} equals, in available energy content, 1,500 tons of coal. If coal were \$4 a ton, U^{235} could compete as a source of power at \$6,000 a pound. This price level is probably possible of ultimate attainment.

The deadly rays emitted by atomic fission may interfere with utili-

acteristically a disease of childhood and young adults. The long bones are most often affected but flat bones are also frequently primary sites. Pain and swelling are usually noted in these cases. Roentgenographically the findings are (a) metaphyseal locations usually, but not always, (b) no early medullary involvement, (c) enlargement of the diameter of the bone shaft when destruction is extensive, and (d)



Fig 63—Roentgenograms of patient in Figure 62 show a soft part mass in right forearm and an area of bone destruction 2.5 cm \times 3 cm in the upper third of the right ulna

periosteal reaction which is very common in these tumors producing parallel "onion-peel" lamellations

The diagnosis of Ewing's sarcoma is frequently erroneously made in childhood due principally to the sole reliance on the demonstration of periosteal reaction which is, of course, present in other diseases, non-neoplastic as well as neoplastic

zation of atomic energy for provision of industrial power. Physicians will need to become familiar with methods of detecting damage which may be done to workers who may be exposed inadvertently to these dangerous radiations.

CLINICAL APPLICATION

Rhoads and Solomon stated that to date only two artificial radioisotopes have been proved without question to be of therapeutic value. These are P^{32} with a half-life of 14.3 days, and I^{131} and I^{131} , with half-lives of 12.6 hours and 80 days, respectively. Until recently, only limited quantities of these two isotopes have been available from the costly and time-consuming cyclotron bombardment. Now, existing piles can provide amounts of these isotopes which will be adequate for medical needs.

Of the disorders which can be treated effectively with P^{32} , polycythemia vera alone has been controlled for long periods. In leukemia, some evidence has been found that treatment with P^{32} results in fewer undesirable side effects than occur when roentgen rays are employed in treatment but there is no greater prolongation of life. Radioiodine is notably useful at present only in treatment of hyperthyroidism. Cancer of the thyroid gland, on the other hand, has not been cured by treatment with radioiodine, though a noticeable palliative effect has been apparent in a few cases.

Hall and his associates at the Mayo Clinic have employed radio-phosphorus as a therapeutic agent since 1941. The most favorable results have been observed in treatment of polycythemia vera. Of 103 patients treated to date, 80 per cent obtained satisfactory remissions lasting for from five months to four years. Partial remissions were obtained in the remaining 20 per cent. With recurrence of the polycythemia vera months or years later, remissions were induced a second time after subsequent treatment with the isotope. In treatment of chronic forms of leukemia, remissions similar to those observed after roentgen therapy were induced with radio-phosphorus.

Rhoads and Solomon made the significant observation that "the very fact that two forms of cancer, leukemia with its allied disorders and thyroid cancer are now treated with radioactive isotopes suggests, however, that other types of neoplastic disease may be found to be susceptible in the future. In particular, the synthesis of radioactive elements into compounds which already have a demonstrable physiological effect on neoplastic disease must be explored." They added that it was easy to imagine that radio-isotopes might be provided as a simple substitute for roentgen rays in photography and that it might be possible to provide a safe, simple and inexpensive method of taking ordinary roentgenograms in remote parts of the world where conventional roentgenologic apparatus is not available.

gineering District Group,²² said "A weapon has been developed that is potentially destructive beyond the wildest nightmares of the imagination. It is to be remembered that the energy released in uranium fission corresponds to the utilization of only about 0.1 per cent of its mass. Should a scheme be devised for converting to energy even as much as a few per cent of the matter of some common material, civilization would have the means to commit suicide at will."

This led Yates to remark "Civilization stands in the twilight zone between a possible Utopia and ultimate destruction. Wholesale even planetary death has come to live among us."

Dr. Raymond B. Fosdick, president of the Rockefeller Foundation, stated that the search for truth concerning atomic energy "has today brought our civilization to the edge of the abyss, and man is confronted by the tragic irony that when he has been most successful in pushing out the boundaries of knowledge, he has most endangered the possibility of human life on this planet. The pursuit of truth has at last led us to the tools by which we can ourselves become the destroyers of our own institutions and all the bright hopes of the race."

Fear is a strong factor in our concern with atomic energy and this apprehension should be recognized, Fosdick said. "Now we are face to face with this urgent question: Can education and tolerance and understanding and creative intelligence run fast enough to keep us abreast with our own mounting capacity to destroy?"

At the opening session of the United Nations Atomic Energy Commission, Bernard M. Baruch said "Behind the black portent of the new atomic age, lies a hope which, seized upon with faith, can work our salvation. If we fail, then we have damned every man to be the slave of fear. Let us not deceive ourselves: we must elect world peace or world destruction. Science has torn from nature a secret so vast in its potentialities that our minds cower from the terror it creates. Science, which gave us this dread power, shows that it can be made a giant help to humanity, but science does not show us how to prevent its baleful use. Only in the will of mankind lies the answer. It is a problem not of physics but of ethics."

Furthermore, Albert Einstein has commented on the problem of atomic energy by stating "Science has brought forth this danger, but the real problem is in the minds and hearts of men."

Having faced the fact that atomic energy possesses fearful potential dangers, what can be done about it? McGraw sounded the keynote when he said "We hold in trust a power that is capable of unraveling the very fabric of our civilization. Equally it may be susceptible of development as a mighty force for human welfare. But we have proved the destructive use while the constructive applications are still in the realm of speculation. At one giant stride our scientific and technological development has so far out-distanced our social engineering."

that we have no choice but to turn our full powers of creative imagination to control the forces we have unleashed and to bend them to man's use rather than to his destruction "

Physicians may well stand in the forefront of the ranks which will align themselves in the battle to turn this mighty force from man's destruction to man's benefit

Only now are the first feeble efforts being made in this direction and, as was mentioned in the Lilienthal report ¹ "We are probably no more able to foresee the ultimate fruits of development than were Faraday's contemporaries to understand what would come of the discovery of electro-magnetic induction "

Two great fields exist for beneficial use "the development of atomic energy as a controlled source of power" and "the application of radiations and radioactivities to the growth of the sciences and practical arts" ¹ Atomic scientists believe that "it is probable that the exploitation of atomic energy as a tool for research will outweigh the benefits to be derived from the availability of a new source of power" They think that it would not be astonishing "if the greatest benefit of this program were in fact to lie in therapy for some of the neoplastic diseases, such as cancer, or in the increased understanding of biological systems or of the realities of the physical world, which will in turn open up new fields of human endeavor "

CONCLUSIONS

Nuclear scientists have unleashed a mighty power for evil or for good and every effort must be exerted to make certain that the potentialities for good are those which are developed Already in the field of medicine a number of promising leads have been made for clinical utilization of atomic energy and even brighter vistas open in the field of medical research We physicians must provide leadership in diversion of the enormous forces of atomic energy from warlike to peaceful scientific pursuits, for, as Fosdick has said, this is "the mighty imperative of our time "

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A CONSIDERATION OF CERTAIN DISEASES OF INTERNATIONAL IMPORTANCE

THOMAS B MAGATH

ALTHOUGH it is true that from time to time the importance of certain diseases has varied with respect to world-wide significance, only five have remained on the international list since the earliest consideration of international quarantine at least 500 years ago. This does not mean that there are but five diseases which are of international importance, but rather that public health officials for all these years have concluded that these alone are sufficiently important and amenable to control to justify efforts to keep them within national boundary lines and to justify laws, established by treaty, to prevent their entry into countries which are free of them.

SOME FACTORS IN DISSEMINATION OF DISEASES

Geography, customs, trade routes and wars play important roles in diseases of international import. Throughout historical times records indicate that whenever masses of people moved, because of economic, political or religious pressure or as a result of the desire for new adventures in commerce or because of wars, increases in the prevalence of communicable diseases in the new areas invaded have followed and frequently the introduction of entirely new diseases has occurred. Even the normal flow of traffic has furnished clear-cut examples of extension of disease, such as that of the introduction of measles and its calamitous effect in the Faroe Islands in 1846.

Trade.—One of the most potent factors in the spread of diseases has been the slave trade, the effects on man's body have been equal to those on his moral fiber. It can be stated with certainty that yellow fever, hookworm disease and filariasis were introduced into the Western Hemisphere by the slave trade from Africa and it is likely that other diseases, as well, were introduced by the same method.

Even today the dissemination of diseases due to economic custom and pressure may be observed along the caravan routes of North Africa and the Middle East. Annually as the caravans swing in a southerly direction in the winter, plague follows in their wake, as do smallpox and venereal disease. Quarantine regulations as applied to overland commerce have never been as effective as when applied to the sea lanes where ports of call are limited in number and the frequency of visits is regulated by the number of vessels available.

Pilgrimages.—One of the most important avenues for the spread

of disease has been the pilgrim routes of the Middle East and India. There the pressure of religion manifests itself in the annual urge, like the hormonal urge of birds, to migrate to some particular place where a change of body and soul may be effected. There are many holinesses besides Mecca in those countries and all along those routes one may see evidence of the disastrous effect of disease. Recognizing the potential hazard of these migrations, the countries involved have made treaties designed to control this dangerous situation and thereby have prevented almost completely the spread of disease from pilgrimages in modern times. The regulations are troublesome, exacting and, at times, humiliating to those of certain religious groups, their religious urge must indeed be great to cause them to surmount such a gamut of hurdles in order that they may prostrate themselves before the shrine of their choice.

The basic method of control is exercised by means of a pilgrim's passport. Aside from the entries and requirements which have to do with his political and social status, entries are made relative to the pilgrim's medical history and the steps which have been taken to prevent his being a carrier of disease and to assure his having been immunized against diseases the names of which appear on the international list.

As a rule the pilgrims are assembled in camps and held there while the necessary procedures are carried out. At times such camps contain as many as 30,000 persons. The process starts with a soap-and-water shower bath, frequently the first the pilgrim has ever had, and at the same time his clothing and baggage are sterilized with steam. He is given a medical examination and, if lousy, his hair is shaved and he is sprayed with delousing agents. He is then immunized against the quarantinable diseases indicated for the region and detained until he is immune and has passed through the period of incubation of the diseases in question. On his return trip the process is repeated, in so far as examination, delousing and bathing are concerned, and he is detained for a time greater than the incubation period of plague and cholera. Now that yellow fever has reached the east coast of Africa, interest is being centered on that dread disease and means of preventing its spread are being imposed on travelers to Mecca from areas across the Red Sea and the Gulf of Aden.

It will be at once apparent that the imposition of such measures is unpractical and unnecessary in the normal course of world trade and that such measures, if instituted, would restrict international commerce to such a degree that the public would not tolerate it. The urge to trade is probably not so great as the urge to follow religious customs, as evidenced by the fact that, in regard to his religious urge, a sacrifice appears to be great enough to deter the believer from reaching his objective.

INTERNATIONAL QUARANTINE

Origin.—Although international attention to the spread of disease by means of transportation has been evident since Biblical times, when a quarantine against leprosy existed, and while Justin probably issued some quarantine regulations, it was not until the last quarter of the fifteenth century that the word "quarantine" was used and that definite regulations were promulgated. This was done in Venice and was followed by publication of a more formal code in Marseilles. Plague had invaded Europe from the Levant in the fourteenth century and its ravages had been felt by the rich and poor alike. It was not until the early nineteenth century, however, that a broadened interest in international diseases caused the first conference on the subject to be convened in Paris in 1851. By then yellow fever had appeared in Spain and cholera had invaded Europe and America. At first, measures were instituted against plague, then cholera and yellow fever and finally, in 1920, exanthematous typhus and variola. There are some regulations governing leprosy and anthrax with reference to the United States, but those pertaining to leprosy do not apply to nationals and those pertaining to anthrax apply only to possibly infected bristles. In an attempt to control psittacosis, traffic in psittacine birds is also regulated.

Quarantine regulations in the United States were first issued a century before the Declaration of Independence by the colony of Massachusetts Bay against a plague, probably yellow fever, in Barbados. The first detention hospital was established in 1757 at Rainsford Island but the first basic legislative act was not passed until 1893. This law has been the controlling measure against the introduction of disease to our shores until the law of 1944, which did not depart much from that of 1893. Modernization of both laws and practices of quarantine has been so slow that medical knowledge and epidemiologic information often have been far in advance of practice.

Those nations which are separated from others by long reaches of ocean have always relied for protection on the time it required transportation to bring new populations from countries in which exotic diseases were present. Generally speaking, the elapsed time of travel by boat from Asia, Africa or Europe to America allowed the development of most cases of quarantinable diseases to take place in passage so that when the boat docked, the seriousness of the illness was at once apparent, quarantine measures could then be applied without the necessity of exhaustive search.

As traffic has become speedier, the need for additional measures has become increasingly evident. Some cognizance of this was observed in the deliberations of the Health Council of the League of Nations and a practical application of modern knowledge was made in the Far East. This application consisted of a system of reporting

the presence of quarantinable diseases promptly by cable and radio to a station in Singapore and redistributing the information from there to various points in the Far East. A similar system was inaugurated in the Western Hemisphere under the auspices of the Pan-American Sanitary Conference, but the system was slow because of the method of reporting, consolidating and republishing information.

During the period just shortly ended, the United States and other countries have made the bill of health, a fifteenth century invention, the basis of quarantine practice, and in the United States its use was not abandoned until after the report, in 1944, of the Interdepartmental Quarantine Commission. Long ago all the principal countries had concluded that it was necessary to know about sanitary conditions at ports of departure before the boat arrived with the information on its bill of health. Accordingly, consuls have been reporting important facts about ports of the world by mail or cable and these reports reach official hands long before the bill of health, although even reports of consuls are sometimes delayed in getting into the hands of the official who must take preventive action.

Recommended Practice.—It should no longer be necessary to make a plea for some form of rapid communication of facts concerning the prevalence of important communicable diseases so that countries may set up quickly the proper screen against them. The rapid flight of airplanes and the anticipated speed of boats link all countries together in terms of time. Certainly knowledge of world-wide distribution of disease is one basis for control in international traffic.

The Interdepartmental Quarantine Commission proposed a radio network with focal points at Singapore, Moscow, Alexandria, Geneva and Balboa. There the reports made at weekly intervals from the respective areas would be consolidated and rebroadcast the next day. Under special conditions of epidemics the airways' radio systems would be used for information relative to individual plane flights.

Next to general information about diseases prevalent at given ports, specific information about the passengers is necessary. At present such information is at best haphazard and traffic is slowed up for all because specific information is not at hand. It is necessary to know two facts about each passenger in international traffic: (1) in what countries has he been during the last two weeks and (2) when and against what diseases has he been immunized. If a simple card showing these facts were carried by each passenger in international traffic, an official could tell at once what action to take with reference to each. If by international agreement immunization procedures were to be required, when indicated, before travel was allowed, little action would be required with reference to most passengers. Those residing for two weeks prior to passage in well-sanitized countries and in countries free of quarantinable diseases would require no inspection and if in

munization against smallpox were required, no hazard whatsoever would exist.

The following rules, if applied to countries in which reasonable sanitary standards prevail, would suffice to protect citizens in one country from introduction of quarantinable diseases from other countries

A. To be detained for observation

- 1 Persons exposed to pneumonic plague within seven days before arrival.
- 2 Persons, unvaccinated against or nonimmune to yellow fever, who departed, less than six days before arrival, from an area in which epidemic yellow fever was prevalent.
- 3 Persons who have been exposed to smallpox within fourteen days before arrival and who have not been vaccinated within the preceding three years and refuse vaccination on arrival

Detention of persons in the foregoing categories need not be in a hospital but persons in the second category should be required to remain behind screens

B To be released under surveillance

- 1 Persons who departed less than six days before arrival from an area in which endemic yellow fever occurs and are unvaccinated or non-immune
- 2 Persons who arrive in less than five days after departure from an area in which epidemic cholera is prevalent and who have not been immunized.
- 3 Persons who have been vaccinated on arrival, who have been vaccinated within the preceding three years and who have been exposed to smallpox within fourteen days before arrival.

Transmission of Insect Vectors by Airplane.—With the advent and expansion of traffic by air, new hazards came to the attention of health authorities. Not only could passengers be transported to new countries during the incubation period of a disease while they exhibited no signs or symptoms, but it was thought that the plane itself would act to transmit vectors (insects) of disease from country to country. The first regulations designed to prevent the occurrence of such a catastrophe as might result from transmission of vectors was issued by the United States Public Health Service. If its action was not based on sound reasoning, at least the Service must be given credit for forward thinking. The regulations were based on the theory that *Aedes aegypti* infected with the virus of yellow fever might board a commercial plane and give rise to an epidemic of yellow fever in the United States and that *Anopheles gambiae* might be implanted in this country by similar means. In neither instance does the theory appear likely to be true. In the first instance the theory was apparently based on a lack of evaluation of the factors which would be necessary before an outbreak of yellow fever could take place. It did not reckon with the habitat and flight range of *Aedes aegypti*, which preclude the likelihood of spreading yellow fever by plane. In

the second instance the theory was based on the notion that *Anopheles gambiae* arrived in Brazil by plane. It now appears this was not the case but that fast French avisos actually were responsible for the act.

As a result of careful study and evaluation it now appears that the airplane has never been responsible for the transmission of a new insect vector of disease into and its implantation in a country, even in the absence of deliberate preventive measures. Such cannot be said with any degree of certainty with reference to agricultural pests and it is here that defense mechanisms must be set up. The use of the freon bomb with pyrethrum has proved to be effective against many types of vectors which might transmit diseases and which might be suggested as possible stowaways. However, against agricultural pests there has not been established as yet a simple or even an elaborate effective barrier.

DISEASES OF INTEREST DURING AND AFTER WORLD WAR II

With the approach and development of World War II a number of other diseases besides those listed as quarantinable became the subject of wide interest and anxiety. It was necessary to explore the theory that the extreme rapidity of travel which would bring great masses of men and women into new countries might affect the health of a great many people, so that, for a while, a kind of hysteria gripped the country. Physicians and others began to speak of, and publish dire predictions of, serious epidemics and widespread disease. Public concern eventually forced the three Surgeons General to take some steps which they knew were unnecessary and of little value. A careful consideration of the epidemiologic behavior of the various diseases and a knowledge of the measures which could be applied to control them under military authority should have given more sense of security than was exhibited. A review of the results may now be used to demonstrate the effectiveness of the measures employed and the nature of certain diseases.

Plague.—Plague did not occur among any of the armed forces of the United States, hence it was not brought to our shores by this personnel. As a matter of fact only four persons suffering from plague have been brought to the United States since 1924, the last one more than thirteen years ago. Plague is, however, prevalent among syphatic rodents in at least twelve states and during the war appeared twice in Tacoma in rats. The danger rests not so much in introducing a person who has plague as in introducing infected rats. This is almost entirely a problem of surface vessels, although with the increase in number of cargo planes, the possibility of introduction of plague carrying rats in this manner must be given more consideration than in the past. Vaccine against plague was used in a few selected places.

The frequent difficulty in differentiating this tumor from osteomyelitis should be emphasized. Since histologic identification may be impossible after radiotherapy, it is imperative that no irradiation be given until diagnosis has been established by biopsy.

TREATMENT—Radiation therapy is indicated. Surgery is not usually employed.

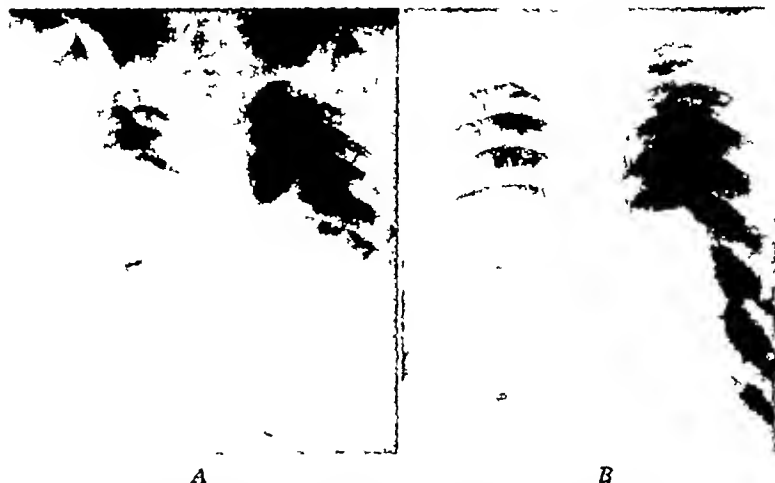


Fig 64—Angioendothelioma, metastatic in lungs (A. L., male, aged 9 years). The primary lesion in the sacrum occurred at the age of 8 years. This responded well to radiation. The pulmonary lesions (A) responded poorly to irradiation therapy. A bilateral pneumothorax (B) occurred during the course of treatment.

Metastatic Bone Disease.—Osteogenic changes may appear in neuroblastoma, retinoblastoma and leukemia, but these usually may be differentiated from primary bone tumors by clinical and other corroborative data, in each individual disease.

NEOPLASTIC DISEASES OF LYMPHATIC AND BLOOD-FORMING ORGANS

The neoplastic diseases of these tissues are leukemia, lymphosarcoma and Hodgkin's disease.

Leukemia—At the onset this disease may simulate the ordinary acute upper respiratory illness of childhood. Among the clinical findings in leukemia are bleeding in the skin, as evidenced by varying degrees of purpura, and into the mucous membranes, and occasionally profuse hemorrhage may ensue. Dyspnea may be present if there is a mediastinal mass or leukemic infiltration. The temperature may be elevated in acute cases. Lymph node enlargement, local or general, is a variable physical finding. Pain in the long bones may or may

there is not good evidence that it played any role in protection of the armed forces. The liberal use of DDT in rat runs and the excellent programs of rat control of the Army, Navy and United States Public Health Service played an important role in preventing the spread of plague. The most promising measure designed to prevent the spread of plague is the campaign of the United States Public Health Service to insist that ships and boats be so built that they cannot harbor rat colonies. It is unfortunate indeed that the Navy did not earlier accept this program although naval craft are rarely permitted to harbor rats.

Pneumonic plague was not a problem in the war and fortunately its occurrence for some years has been confined to small areas in Northern China.

Cholera.—The armed forces escaped cholera during the war and would have had no cases yet had it not been for a group of fourteen men who, disobeying all regulations, acquired the disease in China after the close of hostilities. All personnel going to cholera-infested areas were vaccinated and the evidence clearly favors the conclusion that the procedure was effective. The danger of implanting cholera in this country is small, the numerous hospitals, the well-sanitated water supplies and the increasing number of water carriage sewage disposal systems preclude epidemics of this disease. The attention paid to water and sewage in the armed forces should have allayed the fears of any apprehensive individual. No person suffering from cholera has entered the United States during the last twenty-five years.

Yellow Fever.—Yellow fever was not experienced by the armed forces. At the beginning and before the pattern of the war was determined, there was justification for the universal use of yellow fever vaccine in the Navy and its general use in the Army. After that, however, there was little justification for its use although it was late in the war before the order was modified. Our troops were never in areas in which yellow fever was present. The coastal cities of South America and Africa are free of the disease, and the Orient and India have never known its presence.

Typhus Fever.—Typhus fever, because of its prevalence during World War I, was greatly feared and elaborate precautions were taken to prevent its occurrence in the armed forces. Vaccine was the chief weapon of defense and it proved to be highly effective. Although masses of the forces of the United States were frequently exposed to the disease in severe epidemic form, only sixty-three members of the armed forces contracted the disease and almost all were but mildly ill. Later the use of DDT protected the public and prevented the spread of disease. In countries like the United States, where soap and water are plentiful and reasonably clean clothes the rule, epidemics of typhus should not occur, and since only six persons suffering from

fever, with 12,634 recorded cases, presented no international problem

Dengue Fever and Bacillary Dysentery.—There is no way to estimate the number of cases of dengue fever and bacillary dysentery which occurred during the war. Dengue fever has occurred in epidemic form in the United States several times and is transmitted by mosquitoes of the genus *Aedes*. Bacillary dysentery has been ever-present. Both diseases played disastrous roles during the war, but the nature of these illnesses does not justify their being treated as quarantinable diseases.

Filariaasis.—Of the many infections caused by helminths, surprisingly few were encountered in large enough numbers to make consideration of them important from a public health standpoint. Two in particular caused widespread comment: filariaasis and schistosomiasis. One of these infections was caused by *Wuchereria bancrofti*, this infection together with those caused by all other filarial worms was diagnosed 13,862 times. This number is subject to considerable doubt as to its accuracy, for in the group the diagnosis was made more often from signs and symptoms than from positive identification of the worm. As a matter of fact identification of the worm was rarely accomplished. In perhaps a half dozen the microfilaria of *Wuchereria* was identified and in some, adult worms were found in lymph nodes removed for biopsy. An unknown number were diagnosed on the basis of signs and symptoms and a positive skin or precipitin test. Most of the total number of infected persons have now been declared to be free of signs and symptoms of infection and almost none now have microfilariae in their blood. Two cases of infection by *Loa loa* and one by *Onchocerca* were identified. In a few, *Mansonella ozzardi* was found. There is none in position to infect others and the disease is, therefore, not a public health menace in the United States. In so far as filariaasis is concerned, World War II did not serve to spread the disease as much as did a few boat loads of slaves brought to Charleston, South Carolina, years ago. The fact that it requires a group of heavily infected persons living in a restricted area to establish a focus for dissemination of *Wuchereria bancrofti*, definitely limits the possibility of establishment of new areas removed from already existing endemic areas.

Schistosomiasis.—Schistosomiasis caused by the three species which affect man was observed in American service men and women and was the other helminthic disease to create great concern. Only a few infections due to *Schistosoma mansoni* and *Schistosoma hematobium* were diagnosed. However, about 1,672 cases due to *Schistosoma japonicum* were observed. Fortunately most of the infected persons have recovered but some are still excreting ova. There are no known cases in North America in which the cercariae of either *Schistosoma japonicum*

cum or *Schistosoma haematobium* are able to develop and it is, therefore, unlikely that these worms can become established on this continent. On the other hand, there are snails of the genus *Tropicorbis* in which *Schistosoma mansoni* can develop. They are restricted to areas in the South but the possibility of their becoming infected in nature seems at present to be remote. Persons harboring *Schistosoma mansoni* have entered the United States many times before the war and no area of endemicity has yet been established.

Intestinal Parasites.—There were many instances of infection of the gastro-intestinal tract by parasitic worms in the armed forces. Even the approximate number will never be known. Certainly there were several thousand cases of ascariasis, trichuriasis and uncinariasis. The infections were, for the most part, light and clinical symptoms were usually lacking. These diseases are not propagated unless certain physical factors exist and sanitation is minimal. Where conditions are suitable, these worms are already present in the population of North America and the addition of the worms from overseas will not materially affect the situation. This is true except in reference to one species. *Ancylostoma duodenale* has not been present in the United States, or at least it has been rarely encountered. Infection with it is usually more severe than that with *Necator americanus* and its introduction by members of the armed forces may presage a more severe form of hookworm infection in the years to come.

SUMMARY AND COMMENT

From the foregoing considerations it may be concluded that diseases whose etiologic agents have intricate life histories have a strong tendency to remain fixed geographically, and even the mass movement of people into and out of such areas does not result in implantation of these diseases in new areas if modern preventive medicine can be practiced. On the other hand, since traffic and commerce do tend to spread disease, carefully evaluated barriers must be erected and enforced to safeguard those countries which are free of such diseases. The barriers associated with the air routes have so far been as effective as those associated with the sea lanes in preventing the spread of diseases, land routes are still the chief means for spread.

World War II furnished an excellent test for modern preventive medicine and sanitation. Carefully maintained immunization procedures were remarkably effective. This war, unlike all others, did not seriously spread disease and while individuals did contract exotic diseases, the danger to the public health of North America from these persons is indeed small.

Physicians should be alert to detect and treat members of the armed forces and others who lived overseas and who may now be suffering from exotic diseases. However, physicians and the general public may

be assured that this country is not seriously menaced by them and that no new plagues have been introduced to these shores. Public health officials should strive to maintain their guards on a scientific basis and to eliminate all unnecessary procedures. Usually diseases of international significance, unlike religious and social philosophies, apparently follow Kipling's notion that, "East is East and West is West, and never the twain shall meet."

THE SYMPTOMS AND DIAGNOSIS OF DUODENAL ULCER

ANDREW B. RIVERS AND MAURICE H. STAUFFER

INTRODUCTION

Incidence.—Duodenal ulcer is one of the most common of all organic causes of indigestion. Ivy estimated that there are approximately 1,500,000 persons in the United States more than thirty years old in whom peptic ulcer develops during a period of ten years. On the basis of necropsy and roentgenologic studies, it is estimated that 10 to 12 per cent of all the population are afflicted with a peptic ulcer at some time during their lives. In a ten year period the diagnosis of duodenal ulcer at the Mayo Clinic was made 25,548 times. Of this group of patients, 85 per cent were men. There was a much higher incidence of duodenal ulcer than gastric ulcer, in the ratio of 13:1. This disproportion in favor of duodenal ulcer has always been high in the United States. On the European continent this difference is not so marked. In Stockholm, Ihre and Muller reported the ratio of duodenal ulcer to gastric ulcer to be 3.5:1. This difference has been associated with the belief that gastric ulcers are most common in Europe because of the nutritional disturbances.

Age.—Eusterman studied the age of patients at the onset of symptoms among 701 persons who had duodenal ulcer. The greatest number of patients stated that their symptoms had begun when they were between twenty-one and thirty years of age. Next in frequency of occurrence were those ulcers causing symptoms when the patients had been between thirty-one and forty years of age. The same ages applied to both men and women. Kennedy has shown, however, that it is not unusual to find duodenal ulcer as the explanation for the dyspepsia of which children complain. Acute ulcers occur in the newborn. These lesions may be duodenal or gastric in situation. They may perforate or cause hemorrhage.

Periods during Which Duodenal Ulcer Is Likely to Become Reactivated.—It is well known that duodenal ulcer seems to have a tendency to become reactivated during the spring and fall. This feature is a very striking manifestation in a high percentage of cases. The reason for this has never been shown clearly. One idea has been advanced by De Langen, who hypothesized that during these seasons, in which there is a wide variation of climate, there also is a fluctuation in the tone of small gastric and duodenal blood vessels. He believed that this may give rise to a spastic condition of these vessels, and that such a condition favors the formation of an ulcer. This tendency

for seasonal variation in symptoms frequently is lost as the ulcer becomes complicated by penetrating or obstructive characteristics. During periods in which patients have respiratory or other intercurrent infection, ulcers also are likely to become active. Of greatest importance in determination of the period of reactivation of ulcer seems to be the factor of emotional tension. Ulcer exhibits a remarkable tendency to become reactivated during periods in which the patient is subjected to much worry or nervous fatigue. As this emotional crisis subsides, the symptoms frequently disappear rapidly. This should always be kept in mind when the physician is advising surgical treatment for these patients. Often, if these people can be maintained through a particular trying period of their life, they may never experience return of their symptoms. Dietary errors and the abuse of tobacco and alcohol also may precipitate an attack. Prolonged periods of overwork, mental or physical, with loss of sleep resulting from late working hours, may at times precede a period of reactivation of ulcer. The relationship of the smoking of tobacco to a duodenal ulcer has always been a debated point. There are a few patients who do not use tobacco but in whom an ulcer develops, there are others who become well while they are continuing to smoke. It is interesting to learn of some physicians who refuse to treat patients who continue to smoke, since they feel that the results are so poor that their therapeutic failures eventually may discredit their reputations.

ACUTE DUODENAL ULCER

It is generally presumed that acute ulcers of the duodenum produce no symptoms except when they are responsible for acute perforation or hemorrhage. The gastroscope has yielded much information about the importance of shallow, intragastric lesions in the production of symptoms. That is, there is often a direct parallelism between the varying severity of symptoms and the varying intensity of these pathologic processes in the stomach. The duodenal mucosa, however, cannot be explored by visual methods of this type, so that it is likely to be assumed that no such lesions are present in this region. Such, however, is not the case, for it is known that certain shallow duodenal lesions of the type which characterize duodenitis are quite capable of producing definite symptoms, and that these lesions may be formidable in their complications. W. J. Mayo, Judd, Nagel, Wellbrook and one of us (Rivers) have described such lesions. The intimate mechanism responsible for distress in the presence of shallow duodenal lesions such as characterize duodenitis, or the distress caused by an acute ulcer, may depend, as does the mechanism of simple uncomplicated chronic duodenal ulcer, on factors associated with the ulcer rather than on the ulcer itself. Hyperacidity and hyperspasticity may furnish stimuli from inflamed tissues which should be fully able to be

interpreted as pain. Gross hemorrhage and acute perforation may be the first signs of the presence of one of these shallow duodenal lesions. Diagnosis may be extremely difficult because the lesions usually are too small to change the mucosal pattern enough to be visible in the roentgenologic examination. It is well to remember the possibility of the existence of such lesions, however, when the history is suggestive of peptic ulcer, when the roentgenograms show no signs of ulcer and when gastroscopic investigation shows no intragastric cause for complication. Acute ulcers of the duodenum which follow burns have been described by Curling. These ulcers generally are small, single or multiple lesions which often result in extensive hemorrhages. As a rule, such lesions are found to occupy the same position in the duodenum as that at which a chronic ulcer most frequently is situated. Perry and Shaw reported twenty-nine such cases. In seven, perforation, and in thirteen, gross hemorrhage, was considered to be the cause of death.

CHRONIC DUODENAL ULCER

General Considerations.—The general characteristics which we shall consider as being indicative of duodenal ulcer may be applicable to gastric ulcer as well, so long as the two conditions are uncomplicated. On the basis of the history alone it is frequently impossible, under such histopathologic nature of the lesions, to distinguish between the two conditions. There are certain differences in symptomatology which occasionally permit the making of suggestive diagnoses, but often a roentgenogram is essential to accurate localization of the lesion. Patients who have gastric ulcers often find that distress originates within twenty minutes to an hour after ingestion of a meal, this distress may disappear before the next meal is eaten. This sequence of events constitutes the so-called food-comfort-pain-comfort rhythm. The situation of the distress caused by gastric ulcer generally is indicated as being poorly localizable, but usually it is somewhat to the left of the midline. The pain of duodenal ulcer often is felt slightly to the right of the midline, and as a rule it arises two to three or four hours after the meal, to persist until the next meal, unless it is dissipated by the ingestion of food or soda or milk. These events constitute the pain-food-ease sequence. In about 25 per cent of instances, however, the two syndromes are indistinguishable until the ulcer burrows deeply into the gastric or duodenal wall. At such a time the syndromes assume a different character, and by careful analysis of data obtainable by the history the two lesions generally can be distinguished with ease. The reason for this is that when ulcers reach serosal tissues or spread their inflammatory reactions to periduodenal or perigastric regions, they usually cause the pain to shift into secondary areas, this manifestation, if it is utilized in diagnosis, enables the physician to arrive at accurate localization of such lesions. It should be remem-

bered, however, that just as the roentgenologic examination may never be a substitute for a well-taken history, neither should the history ever be considered an adequate substitute for a roentgenogram. The two must be used to corroborate and assist each other. Duodenal ulcer, especially prior to the development of complications, produces a remarkably precise group of sequences which pertain not only to pain, but also to the general behavior of the syndrome as a whole.

Periodicity and Intermittency of Symptoms.—It is extremely rare to find a patient with a peptic ulcer in the duodenum whose symptoms do not occur in cycles. The periods of distress at first are so brief and so mild that they cause very little concern, and they are forgotten almost as soon as they have passed. Often, direct questioning is required to bring out the fact that such a patient may have experienced such episodes of indigestion, dating back to youth. Sometimes there may have been two or three years during which periods of distress and periods of comfort alternated. Then, for twenty or thirty years, there was uninterrupted good health, which was followed in old age by recurring indigestion with symptoms suggestive of the presence of peptic ulcer. At other times, a few years of reappearing dyspepsia in the early life of the patient may be all the evidence available to mark the period of distress when a duodenal scar is discovered during routine examination later in life. An illustrative case follows.

We are reminded of such an experience in the case of a minister who presented himself for examination at the age of seventy-two years because of prostatic obstruction. Having been registered in a section devoted mainly to gastrointestinal disturbances, he was asked during his preliminary consultations about complaints referable to the stomach. When he said these had been present, he promptly underwent roentgenoscopy, at which a duodenal deformity was reported. Later, we advised him of the finding, and we were surprised to learn that he had not experienced indigestion for at least forty years. We were naturally interested to know by what means he had been treated to effect such a remarkable cure. He said he had not been treated at all, but his story was significant. He was a farmer boy. After his marriage in his early twenties, he moved to town and started a small store. His wife and he worked, and they saved some money. He had always wanted to preach, so he sold the store, took his savings, and began his preparation for the ministry. This took several years longer than he had expected. Several babies were born, which meant that he had to work evenings to get enough money to live. There were several years of privation, some illness and some hardships. It was during this period that the symptoms typical of peptic ulcer developed. With the completion of his studies he was given an assignment in a rural church. He moved his family to the vicinity; with the re-establishment of his feeling of security his symptoms disappeared and the ulcer healed completely and permanently.

After complications, such as chronic perforation or obstruction arise, the syndrome of ulcer frequently becomes less intermittent. Later, this characteristic may be lost entirely.

Pain.—Location—When the patient who has an uncomplicated duodenal ulcer is asked to designate the area in which distress is felt, he indicates this, as a rule, with the palm of his hand as being somewhere in the epigastrium. At times the patient may not be able to be exactly sure of the area on the abdomen to which the subjective sensations are confined. Many patients indicate that the area of pain is situated just below the xiphoid process.

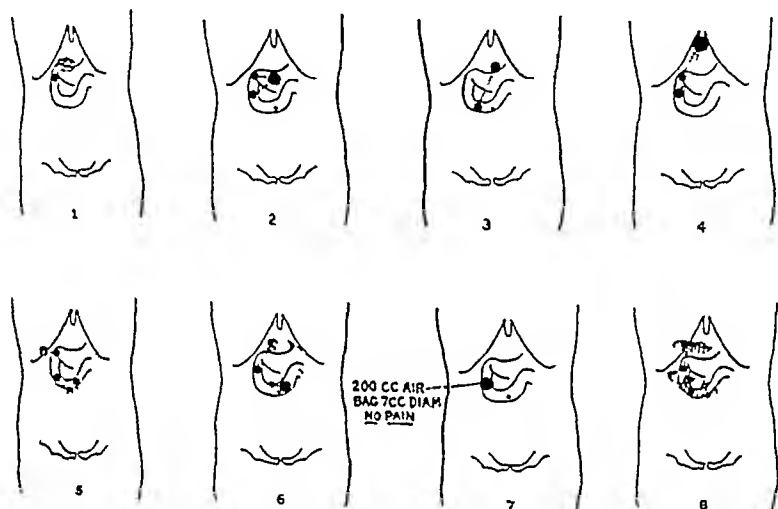


Fig 158—The distribution of referred pain as charted by Bloomfield and Polland after inflation of the duodenum with a balloon, in eight cases. Situation of the balloon is indicated by the solid black dots, the resulting sites of referred pain are depicted by the shaded areas. (Reproduced by permission of the publishers, from Bloomfield, A. L. and Polland, W. S. Experimental referred pain from the gastro-intestinal tract, stomach, duodenum and colon. *J Clin Investigation*. 10: 453-473 [Aug] 1931.)

In experiments carried out by means of a balloon in the duodenum, Bloomfield and Polland found that the pain most often was felt in the midline (fig 158), but when it was not, it usually was felt to the right, above the umbilicus. Many patients, when closely questioned will point to this area as mentioned, somewhat to the right of the midline. There is rarely any extension of pain into secondary areas, such as the thorax or the back, so long as the ulcer remains uncomplicated. At the height of the pain the area complained of is more often designated as being somewhat on the right side.

Character of the Pain—The pain is extremely variable in intensity, and it is variously described by those who experience it. It may be

described as a sensation of pressure, a feeling of fullness or discomfort, a burning feeling, or a sense of weight or oppression. At times it may be designated as a dull, deep-seated boring sensation which, although not very severe, may be rather demoralizing in systemic repercussions. With this there is a feeling of exhaustion, buckling of the knees and a strange fear reaction. This is not caused by the severity of the pain. But the patients often are far more concerned about these associated disturbances, which may be splanchnic in origin, than they are about the pain proper. With the termination of the distress, these reactions promptly disappear, and the patients carry on their activity in their usual vigorous manner.

At times the pain is severe. It may be likened to "tying the stomach in a knot." The distress often is associated with a burning sensation in the substernal area. Often there is an unpleasant sensation of emptiness akin to an exaggerated feeling of hunger. Moynihan referred to this as a "hunger pain." It may be accompanied by acid eructations into the throat. Salivation is a common experience, frequently such a patient drools at night, so that in the morning his pillow is saturated. Occasionally there occurs a sudden evacuation of a large amount of watery alkaline content of the esophagus which has accumulated above the spastic cardiac sphincter. This has been referred to as "water brash" or "pyrosis."

Although there may be great variability in the character of the pain in different persons with duodenal ulcer, the same character of distress to which he has become adjusted is often maintained in the individual patient. It is only when changes in this distress occur that he is likely to consult his physician. As a rule, there is no extension of the pain of uncomplicated peptic ulcer. Nausea and vomiting occasionally may accompany the pain of ulcer. They may occur even in the absence of signs of obstruction.

Time of Pain—The patient with a gastric ulcer whose stomach is empty is often more likely than not to be without distress. The patient who has a duodenal ulcer finds that his most comfortable period is immediately after the meal. During the early course of the disease distress may arise only after the heaviest meal of the day, but as time goes on symptoms commonly are present with clocklike regularity after every meal. Later in the course of the disease there is often a period of distress at 1 or 2 o'clock in the morning. Often, this awakens the patient with such regularity, at the same time each succeeding night, that he "can set the clock" by its occurrence.

The size of the meal may influence the time of onset of the pain to some extent. A large meal may delay the time of distress. After the ingestion of a small meal or if only liquids are taken, the pain may originate within an hour. Certain types of food or drink may influence

not be complained of Splenomegaly is almost constantly noted, in some cases enlargement of the spleen is considerable and in others it is minimal The liver may or may not be moderately enlarged but it seldom attains the proportions of the leukemic spleen Stomatitis is an inconstant finding Renal enlargement has been observed, particularly in small infants Asthenia is invariably a late symptom

The diagnosis may be made at times by the peripheral blood findings alone For accurate diagnosis in some cases, however, a sternal marrow examination may be required Peripheral blood studies will show anemia, thrombocytopenia, leukocytosis of varying degree or at times leukopenia, agranulocytosis is frequent Mononuclear cells are present in rather large numbers and are all of the nongranular type -

Most of the cases observed by us in children have been of the acute type although a classification into acute lymphatic or acute myeloid type is very difficult in many if not in most cases, even by experienced hematologists

Clinically, leukemia must be differentiated from (a) other blood dyscrasias and conditions causing bleeding, (b) other diseases causing lymph node enlargement like tuberculosis, (c) intrathoracic tumors such as thymoma, lymphosarcoma and Hodgkin's disease, (d) intra-abdominal tumors such as Wilms's tumor, neuroblastoma, polycystic kidney, and (e) conditions producing persistent dyspnea, such as tuberculosis, cardiac disease and asthma

The more common diseases from which leukemia must be differentiated hematologically are

Thrombocytopenic purpura This presents a difficult differentiation at times Depression of the megakaryocytes in the marrow may be severe in both leukemia and thrombocytopenic purpura, but there are significant abnormalities in the other marrow constituents in leukemia which are not present in thrombocytopenic purpura

Pertussis The peripheral blood may at times show a mild to moderate leukocytosis with lymphocytosis, but the clinical findings and, if necessary, the study of a sternal marrow smear will aid in the differentiation

Acute infectious lymphocytosis Systemic symptoms are absent except at the onset of the disease There is no lymph node enlargement, splenomegaly, hepatology or anemia A marked leukocytosis with a high percentage of small normal lymphocytes is found The bone marrow shows an increase in the number of small lymphocytes

Infectious mononucleosis Systemic symptoms with fever may last as long as three weeks Occasionally purpura and stomatitis simulating leukemia may be alarming manifestations Lymph node enlargement and splenomegaly occur frequently, but hepatomegaly is rare A mild leukocytosis with lymphocytosis is present, the lympho-

the severity of the distress, but they seldom influence greatly the period of relief which follows the meal, although alcohol or wines may cause some distress shortly after the meal

Patients often adopt a liquid diet because they have found that by the frequent use of only small amounts of food they may avoid the episodes of pain entirely

Methods of Obtaining Relief of Pain—Patients who have duodenal ulcer soon learn that their pain continues until the next meal, which then promptly stops the distress. This leads them, between meals, to eat small amounts of food or to drink some milk, which quickly dissipates the distress. Not infrequently they make the discovery that they can prevent the onset of pain by taking a biscuit or a cracker or some milk, so they form the habit of eating between meals. These patients often carry a few crackers or some malted milk tablets with them as a means of obtaining relief if the pain should arise during the day. When they retire at night, they will place a glass of milk beside their bed in order to be able to stop the distress which is so likely to awaken them at 1 or 2 o'clock in the morning.

The pain may be relieved by the drinking of a glass of water or by belching, but as a rule, ease of symptoms obtained in this way is of short duration.

The use of some alkali is found to be a satisfactory means of terminating the pain, and this frequently is accomplished more rapidly if the alkali is of the effervescent type. The combination of belladonna and a barbiturate also will stop the distress, although the action of such a combination is less rapid than that exerted by an antacid.

Lying down may be followed promptly by some relief of symptoms. Some of the patients will lavage their stomachs at night before retiring or during the time of their pain, if retention is present, lavage is especially likely to bring satisfactory relief. The institution of a regimen which includes rest, frequent ingestion of bland food, and the taking of antacids and sedative agents usually terminates an episode of distress within a few days.

THE COMPLICATIONS OF CHRONIC DUODENAL ULCER

Pyloric Obstruction.—*Gastric Retention*—When confronted with the necessity of decision as to a course of therapy for the patient with duodenal ulcer who shows signs of gastric retention, the physician should remember that such stasis does not necessarily denote the existence of cicatricial narrowing of the duodenum or of organic involvement of the pyloric sphincter. A considerable number of patients who have duodenal ulcer will be found at one time or another to exhibit demonstrable signs of gastric retention. Indeed, most of the patients will give a history suggestive of transitory difficulty of the

stomach to empty itself. This is not difficult to understand when the proximity of ulcers of the duodenum to the pyloric sphincter and the tendency toward hyperspasticity so noticeable in the pyloric area in most of these patients are considered.

Among the diseases of adult persons which are responsible for organic obstruction in the pyloric region, duodenal ulcer certainly ranks first. At necropsy, Portis and Jaffe found evidence of pyloric stenosis in 11.6 per cent of 120 patients who died of peptic ulcer. Their statistics were published in 1938. It is rather interesting that Gerhardt, just fifty years earlier, estimated the incidence of this complication in peptic ulcer to be 10 per cent. One might think that fifty years of medical progress with its refinements in diagnosis would have resulted in earlier diagnosis and more efficient methods of therapy, thus preventing the development of such a complication. Hurst quoted some statistics which suggest that 23 per cent of patients who have duodenal ulcer actually exhibit some signs of pyloric or duodenal obstruction.

Gastric retention caused by duodenal ulcer may result in several ways. The first of these is dysfunction of the pyloric sphincter. Failure of the rhythmic, smooth functioning of the pyloric sphincter is no doubt the cause of most of the instances of retention noted among patients who have duodenal ulcer. The retention is transitory, although it may persist for twenty-four hours or even longer. The obstruction is not complete. It is more a delay of emptying rather than true retention.

The second type of gastric retention resulting from duodenal ulcer is organic obstruction. This may occur in several ways. Subacute duodenal ulcers may, by their inflammatory reactions, produce enough swelling to block partially the pyloric sphincter of the duodenal bulb. Cicatricial stenosis may cause sufficient scarring, particularly in the large perforating type of ulcers of the posterior wall, to narrow the lumen of the duodenum in the areas contiguous to the pylorus, and this narrowing may in turn cause interference with the passage of the gastric contents into the second portion of the duodenum. Occasionally, such an ulcer actually encroaches on the pyloric sphincter itself, and causes obstruction.

The symptoms of duodenal ulcer are so well ordered in sequence that generally it is possible by means of careful observation to detect the presence of complications early in their development. Thus, if the stomach is unable, whether because of pyloric spasm or cicatrization, to empty itself completely within a normal period, there are usually some changes in the clocklike precision of the previously established syndrome. The "normal emptying time" of the stomach is, of course, subject to some variation. As a rule, there should be no gastric residue after seven to nine hours. In fact, retention of barium after six hours

often is considered to be significant of some degree of delayed emptying

Eusterman has stressed the use of the motor meal, which may indicate obstruction even when the barium passes in the normal time. This consists of a meal which includes meat, raisins and spinach. It is taken between 10 p.m. and midnight. Aspiration of these contents at 8 a.m. is evidence of some degree of pyloric obstruction.

It is difficult to make a clinical classification of the symptoms of duodenal ulcer complicated by gastric stasis because of the extreme variability of the histopathogenesis of these lesions and the variation in sensitivity of the patients who have such ulcers. The symptoms of duodenal ulcer may be initiated by obstruction, on the other hand, ulcers which at operation are found to leave only minute room in the duodenum or at the pylorus for the passage of food may produce no clinical signs of retention. Decompensation of stomach musculature depends on so many factors peculiar to the individual that no definite rules for its establishment can be laid down.

There are certain pathways, however, which the syndrome of duodenal ulcer with retention usually follows, and for the sake of clarity we shall attempt to consider the mutations of this syndrome, depending on the most frequent causes for its production.

Stasis caused by pyloric dysfunction is a complication which usually can be recognized by the detection of certain abnormalities in the behavior of the previously experienced symptoms. The patient with duodenal ulcer who never experiences this symptom is the exception rather than the rule. He may notice, five or six hours after the ingestion of food, that there is an uncomfortable "splashiness," or a "liquid" gurgling in his epigastric or upper umbilical area. It is true that the stomach need not be empty at such a time, but the amount of residue is seldom sufficiently great to produce such a distressing sensation so late after the taking of food. Associated with this there are belching and gaseous distention. Small amounts of sour gastric residue, including particles of food, are regurgitated. In such patients we have often passed a stomach tube eight or nine hours after the ingestion of food, and have recovered 400 or 500 c.c. or more of gastric debris. Frequently, this occurs after the evening meal, sometimes such a patient will report that the day has been a particularly strenuous one, physically or mentally. The brief episode of retention may be followed by similar symptoms for two or three days, or the experience may be an isolated one. The entire cycle may repeat itself several times during the course of a two or three week attack.

During the course of such an episode the pain-food-ease rhythm is obliterated. Soda may relieve the distress, food does not, although the institution of a milk diet for a day or two usually stops retention.

Nausea and a generalized feeling of epigastric discomfort generally are present. Headache may be associated, and the appetite is diminished. There may be excessive thirst or an inordinate desire for some carbonated beverages. These may actually relieve the distress.

The complication is not a serious one, nor should it be confused with organic obstruction, from which it can be distinguished by the history and the results of roentgenologic examination or the ingestion of a motor meal.

Gastric stasis may be the result of chronic cicatrizing duodenal lesions. There are certain instances in which the development of gastric decompensation is slow and insidious. It may be unassociated with any particular flare-up of activity of the ulcer. The symptoms of peptic ulcer may have been present for many years, exhibiting their usual cyclic characteristics. The symptoms may have been mild, and because they yielded to the usual methods of obtaining relief, these patients accepted them as they might a summer storm or a winter blizzard, knowing that patience, and the taking of some milk and soda would soon bring about fair gastronomic weather again. With each succeeding year more cicatrization may have occurred and the ulcer, although it did not exhibit subacute penetrating characteristics, eventually narrowed the duodenal bulb or its neighboring sphincter sufficiently so that retention and ultimately obstruction resulted. The patients gradually began to notice a change in the syndrome. That is, the clocklike precision of the syndrome changed, more nausea and vomiting occurred, distention became troublesome, and food may not have relieved the symptoms. For a time the pain may have become more severe, later, it may have stopped entirely when the gastric decompensation became severe. The patients may have found that they were more comfortable after taking less food. Anorexia may have helped in deciding this, and nutritional conditions and toxemia may have resulted.

The foregoing picture may be the one with which the syndrome begins, but this is most unusual. Convulsions and tetany may be the initial symptoms of this type of ulcer, but, as a rule, they are late complications.

Changes in blood chemistry then will be present. The complications can be detected without difficulty with the aid of the stomach tube, which will show retention, and roentgenograms, which will demonstrate the evidence of obstruction at the pylorus or in the duodenum.

The syndrome has many features in respect to symptoms and progress of behavior which necessitate distinction from carcinoma, particularly if the history is brief and the development of retention is gradual. As a rule, carefully made roentgenograms will settle the problem with

out difficulty. A case in which a duodenal ulcer caused obstruction by insidiously encircling the pylorus may be detailed as an example.

A nun forty-four years old came for examination because of attacks of vomiting. For fifteen years she had periodically noticed distention of her stomach by gas, and a distressing sensation of fullness which reached maximal severity several hours after her meals. She found that the taking of soda from time to time would permit her to go on with her work without any handicap, thus proved to be true until five months prior to her coming to the Clinic. At that time she noticed more fullness and a sense of crowding of her heart forty-five minutes to one hour after her meals. This troubled her more seriously, and sometimes kept her from working. Until seven weeks prior to her consultation at the Clinic, however, she had experienced no vomiting. Since then, however, she had had three attacks during which, for a two day period, she vomited everything she ate. At times she regurgitated food which she had eaten twelve to fourteen hours previously. Estimation of gastric acidity showed values of 52 for total acids and 32 for free hydrochloric acid (method of Töpfer). The roentgenogram localized the lesion in the duodenum. At operation a duodenal ulcer was found which had extended to and encircled the pylorus. The stomach was markedly dilated.

In another case gastric stasis was due to subacute or perforating duodenal ulcer.

A man sixty-eight years old came to the Clinic because of indigestion. He said that this had been present for several years. This distress had been troublesome, attacks would last for several weeks, after which he would have a period during which he was comfortable for some time. He described the distress as a cramplike pain which was epigastric in situation, occasionally it seemed to extend through to the back. He also occasionally had distress which extended upward into the thorax. This distress was severe, the question of coronary disease had been considered as an explanation for it.

The pain was found to be relieved at times by the use of food or alkalis. During the month prior to the patient's coming here the symptoms had been present daily and periodically, the pain had been much more severe. Little relief of symptoms was achieved by the use of food, although alkali occasionally did provide some relief. The distress was so severe at times that the hypodermic injection of opiates was necessary to control it. At times there were days on which the patient would vomit large amounts of food, some of it was food he had eaten from twelve to twenty-four hours previously. Estimation of gastric acidity showed values for total acids to be 64 and free hydrochloric acid, 48 (method of Töpfer). The roentgenogram disclosed a partially obstructing lesion at the outlet of the stomach. In another roentgenogram made later this lesion was localized to the duodenum.

At the operation the patient was found to have a subacute penetrating and obstructing duodenal ulcer situated just distal to the pylorus, with attachment to the lower portion of the gallbladder. An inflammatory mass was approximately 2.5 by 3 cm.

The gastric stasis which is encountered most commonly at the Clinic at present belongs to the group of which the foregoing case is an example. Usually, the ulcer is large and, in addition to extensive involvement of duodenal tissues with cicatrization and periduodenal

involvement in the course of the perforating progress of the ulcer, there is local evidence of marked inflammatory reaction. The combined result of these pathologic processes narrows the duodenum sufficiently to cause an impediment to the flow of gastric content into the lower part of the duodenum. In other instances the ulcer, although exhibiting no perforating characteristics, shows evidence of initiating a widespread inflammatory reaction which in itself is quite capable of causing gastric retention temporarily, at least.

The symptoms, in the presence of either process, usually are similar, although when the latter type of lesion occurs the symptoms of obstruction may still be reversible. As in the case of the previously described group, the symptoms may start precipitously with the signs of retention, although this is a most unusual occurrence. But when it does occur, the history, again, is helpful in suggesting the development of this complication.

Physical examination often will reveal a so-called splashy stomach. At times visible peristalsis is present. Often, tapping of the patient's abdomen over the stomach or the application of a cold wet towel will stimulate the stomach to produce these visible contractions. Generally, marked tenderness is reported in that part of the upper right abdominal quadrant which corresponds to the area of the duodenal lesion.

General Factors Relating to Pyloric Obstruction—TOXEMIA—In addition to the symptoms of pyloric obstruction in itself, there is another group of manifestations of certain systemic changes which are related to obstruction in an indirect manner. These symptoms are caused by changes in the blood chemistry. For many years it was recognized that in the presence of pyloric obstruction there is a symptom complex resembling that of toxemia, and that death often ensues in much the same fashion as it does in uremia due to renal disease. The symptom complex in question often was called "gastric uremia." The symptoms which result from this disturbed blood chemical content are loss of appetite, headache, nausea, muscle twitching, weakness, nervousness and more vomiting. If the condition is severe, actual tetany may develop. Any of these symptoms should be viewed with alarm, and an attempt should be made to investigate the changes in the blood which are actually responsible.

BASIS FOR ELECTROLYTE CHANGES—In 1923 Haden and Orr found that the blood chlorides are decreased in the presence of obstruction situated high in the intestinal tract. More recently, the work of Gamble in particular has cleared up much of the confusion once associated with chemical changes in the blood subsequent to gastrointestinal disturbances. The reader should be left with the idea that the blood chemistry is altered in a link-chain manner because of one factor—loss of the chloride ion in the vomiting of the gastric contents.

To understand the basic biochemical blood changes, they must be represented in as simple a manner as possible. We should start with the fact that the great majority of the total electrolytes in the blood consists of sodium in the form of (1) NaHCO_3 and (2) NaCl . When the stomach secretes hydrochloric acid, which comes from the blood, and this hydrochloric acid is lost in vomiting, more is required from the blood and tissues. This results in low quantities of blood chlorides and dehydration. The sodium which was attached to the Cl is then momentarily unattached, but is quickly combined with the ever-present HCO_3 , and thus the carbon dioxide combining power is elevated, with a resultant increase in the blood pH known as "alkalemia". The consequent conditions thus due to the vomiting arising from pyloric obstruction are (1) dehydration, (2) hypochloremia, (3) alkalemia and (4) azotemia.

AZOTEMIA—This term is used to denote, essentially, an elevated value for blood urea. When it is brought about by the consequences of obstruction it is often called "extrarenal azotemia". When vomiting causes hypochloremia and alkalemia of some degree, there is also an increase in the content of urea in the blood. The reason for this is not well understood, but we can say that the kidney does not tolerate marked changes in the acid-base balance of the blood. Either alkalemia or acidemia may cause renal dysfunction. Occasionally, there will be renal damage without changes in the electrolyte levels, as a rule this is presumed to have basis in dehydration. Thus, as the cause of an elevated content of urea in the blood in obstruction the factors of (1) alkalemia and (2) dehydration are acting on the kidneys. This mechanism should not be confused with renal disease in itself. However, it can be understood easily that pre-existent renal disease will cause these conditions much more quickly and accentuate them to a greater degree than might otherwise be the case. In some cases it will not always be clear whether the azotemia is due to the current change in blood chemistry causing renal dysfunction or whether there was some unrelated previous renal disease. Often, after these marked disturbances, there will be a very slow return of the blood urea to normal. It has been said that urea may accumulate in the intestinal mucosa, experimentally after extirpation of the kidneys. There it might decompose to form ammonia, which would cause gastric irritation and further produce vomiting, in addition to the obstruction.

Method of Altering Biochemical Changes—Since the primary change is loss of chloride, the condition of the blood is best restored by the intravenous administration of solution of sodium chloride. This immediately restores the content of chloride to the blood, decreases alkalemia and aids renal function. Values for chlorides and urea should be as nearly normal as possible before surgical treatment is considered. However, it can be seen that the introduction of sodium

chloride may ameliorate hypochloremia but will also provide an excess of sodium which is not needed. This sodium may not be excreted readily and will still be attached to the bicarbonate radical. Therefore, reduction in the carbon dioxide combining power may be very slow. Eusterman has said that if the values for chlorides and urea are fairly normal, one can proceed with surgical treatment, since because of the afore-mentioned mechanism the somewhat continued elevated carbon dioxide combining power is not a threat in itself (fig 159). Ammonium chloride has been used to introduce chloride into the blood, without the concomitant introduction of more sodium. This is a procedure to be kept in mind when the physician wishes to alter alkalemia.

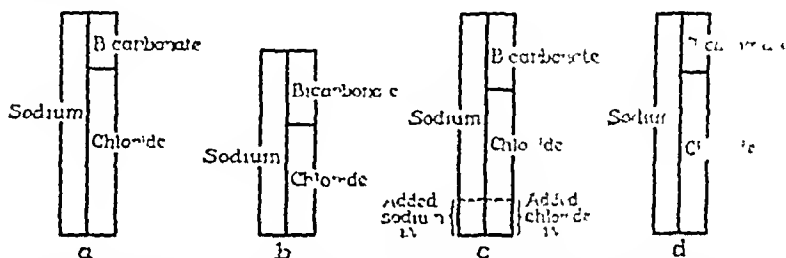


Fig 159—Schematic representation of the proportions of sodium bicarbonate and sodium chloride in blood plasma. *a*, in a normal state, *b*, after vomiting, *c*, after the intravenous administration of sodium chloride but before renal compensation, and *d*, in a normal state again, after renal compensation. In *b* is depicted the increase in bicarbonate after the loss of chloride responsible for the elevated carbon dioxide combining power. In *c* is demonstrated how, after the intravenous administration of sodium chloride, the chloride may be increased relatively to nearly normal, with the carbon dioxide combining power remaining high because of the introduction of sodium with the chloride. The figures are graphic representations only, and are not accurate as to milliequivalent values, concentration or chemical balance.

THREE PRACTICAL LABORATORY PROCEDURES—Practically speaking as seen from the foregoing, three determinations relating to the blood should be carried out to study correctly these problems, namely, determination of (1) the blood chlorides, (2) the carbon dioxide combining power, and (3) the blood urea. These can be done in any moderately well-equipped laboratory, when they are used together these three values will afford the information necessary for further medical treatment and especially enable the physician to bring the patient's blood to the correct chemical status for surgical operation. For a number of years, surgeons have been impressed by the high mortality rates among patients whose blood has not been brought to the proper electrolyte balance preoperatively.

LESS TENDENCY TOWARD ALKALEMIA IN POSTVAGOTOMY AND GASTROINTESTINAL OBSTRUCTION—Bockus has written that he has rarely en-

countered alkalemia in cases of malignant obstruction at the pylorus. This is due simply to the fact that in the majority of cases, malignant obstruction is accompanied by achlorhydria, which means that there is no loss of chloride with its subsequent alkalemia. However, alkalemia does occur in cases in which gastric acidity is present, as it is in a small number of cases of carcinoma. Along this same line of reasoning, it is interesting to note that in the obstruction which sometimes follows bilateral vagotomy there is not this tendency to produce hypochloremia and alkalemia. Such a situation is easy to understand since, in many instances when the vagi nerves are cut completely, there is a complete absence of free hydrochloric acid. Therefore, when patients who have undergone vagotomy vomit because of obstruction at the pylorus caused by imbalance of the sympathetic and parasympathetic nervous control, loss of acid does not occur. This was noted by Dragstedt in 1944. We have seen this unaltered blood picture on several occasions among patients who had pyloric obstruction after vagotomy. Consequently, in such cases the potential threat of alkalemia is not so great, and the gastric contents may be aspirated rather indiscriminately. In summary, since there is not the loss of chloride from the gastric juice after vagotomy and in the presence of carcinomatous obstruction, there is much less tendency toward hypochloremia and alkalemia than there is when duodenal ulcer causes pyloric obstruction.

Nutritional Disturbances—Loss of Weight—Many patients who have chronic pyloric obstruction will experience severe loss of weight. Sometimes this apparent loss actually will represent only dehydration brought about by vomiting and loss of chlorides. Often, however, the loss of weight is not so marked as might be expected. In the majority of cases, pyloric obstruction is rarely complete, generally it is intermittent. It was stated by Emery that in 8 per cent of cases in which complete pyloric obstruction was found in roentgenograms of the stomach, the obstruction was not evident clinically.

HYPOPROTEINEMIA.—It has been intimated by many that the plasma proteins of patients who have pyloric obstruction often will be decreased below normal. This will happen in some few instances. However, we believe it is not common, since so often the obstruction is only partial, so that some quantities of milk or cream, which is high in protein, are able to pass through. A diet which includes milk or cream also may maintain the patient's weight better than expected. But when hypoproteinemia is encountered, it is readily explained on the basis of dietary deficiency, or it may, in addition, be caused by loss of blood in hemorrhage.

VITAMIN DEFICIENCY STATES—Since patients who have pyloric obstruction resulting from duodenal ulcer often subsist for months on a selective diet, it is understandable that vitamin deficiency states may occur. Foods which are especially rich in vitamin C generally will not

pass through the pylorus. Deficiency of vitamin C is important, since it may contribute to additional hemorrhage, and it will delay healing of both the ulcer and the tissues after surgical intervention.

Hemorrhage—Incidence—Duodenal ulcer is the most common among all of the diseases responsible for hemorrhage in the upper part of the gastro-intestinal tract. Wilbur and one of us (Rivers) reviewed the records of 668 patients who came to the Clinic and reported that they had vomited blood, it was found that in 56.6 per cent of cases the hematemesis was caused by duodenal ulcer. Hurst reported that hemorrhage occurred in 25 per cent of patients with duodenal ulcer at the New Lodge Clinic. This corresponds rather closely with the figures reported among patients with duodenal ulcer at the Mayo Clinic. It probably does not represent an accurate estimate of the frequency of occurrence of hemorrhage in the total number of persons who have duodenal ulcer, because only those whose condition is more serious are likely to reach clinics or hospitals. Bockus estimated that the incidence of bleeding in the presence of peptic ulcer probably is a little less than 5 per cent.

Site of Bleeding—Matthews expressed the belief that the bleeding of a duodenal ulcer is more serious than is that of gastric ulcer because the bleeding is more extensive and more continuous. It is generally believed that ulcers situated on the posterior wall of the stomach are responsible for the majority of hemorrhages. The reason for this is thought to be that the posterior wall is often the place of origin of subacute or penetrating, burrowing lesions which cause large erosions in this area without free perforation into the abdominal cavity. As a rule, the question of gross bleeding is related to the proximity of the ulcer to large vessels.

Precipitating Factors—To understand more fully the complications of hemorrhage among patients who have duodenal ulcer, it seems fitting that we should mention some observations concerning these patients which are not, as a rule, kept uppermost in the physician's mind. That is, it seems indisputable that, day to day, duodenal ulcer is encountered most commonly in the tense, ambitious, hard-driving, hard-driven, emotionally labile, never-relaxing type of person. Hence, the implications of this should be kept in mind when the physician sees a patient who has a hemorrhage from the upper part of the gastro-intestinal tract. There are three important precipitating factors in the development of hemorrhage from duodenal ulcer: (1) severe emotional upsets, (2) unusual physical exertion and (3) alcoholism. If these aspects are borne in mind, it is interesting to note these factors in given cases, of which the following fragmentary ones are examples.

A man thirty-nine years old had a severe hemorrhage while he was being unstrung during physical examination for military service.

cytes are typical. The heterophile antibody test is positive in many cases.

Röntgenographic Evidence (Fig 65)—The early findings consist of a subdiaphyseal rarefaction noted especially in the femurs and tibiae. There may be periosteal reaction of the parallel type. Ill-defined, irregular areas of cortical or medullary bone destruction may be demonstrated. These changes are frequently limited to the ends of the long bones.

TREATMENT—The treatment is still palliative. The results from the use of radioactive phosphorus and nitrogen mustards for leukemia of children have been disappointing. Studies on the effects of urethane² are now being carried out.

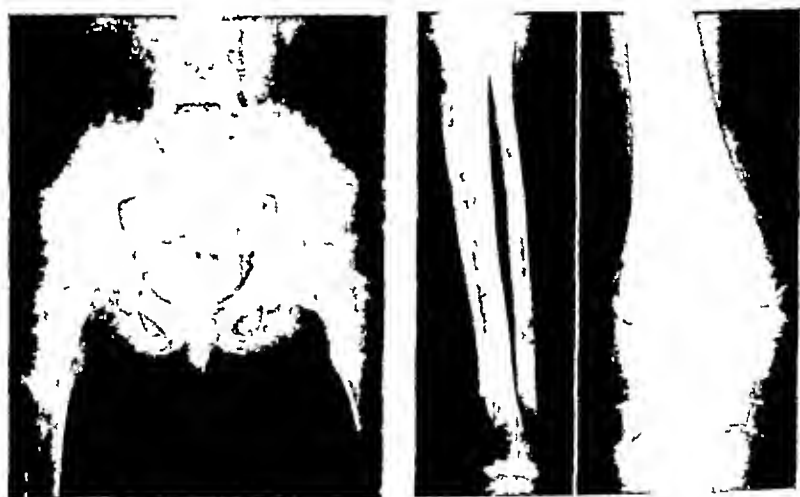


Fig 65—Acute leukemia (J K, male, aged 11 years). Roentgenograms show considerable loss of normal bone density, most marked at ends of shafts of tibia, fibula and femur. Trabeculae are quite prominent.

Lymphosarcoma—Inasmuch as this tumor may occur in any lymphoid structure, it is evident that the symptoms and physical signs depend on the anatomic site of the structures affected. It is not usually encountered before the tenth year of life. The nasopharynx and tonsil, the cervical or any other group of lymph nodes may be involved. I have known lymphosarcoma to have originated in the posterior thoracic lymph nodes, as proved by necropsy examination. The signs for several months were limited to a paraplegia and sensory changes, resulting from extension of the tumor into the spinal canal and cord pressure.

Many cancers simulate other disorders but lymphosarcoma, because of its many selective sites, probably is clinically confused with more

In another man thirty-three years old hemorrhage developed just at the termination of a horseback ride, three months later he suffered another hemorrhage while he was under the strain of a business merger, four months later he had still another severe hemorrhage the night he entered a hospital preparatory to undergoing gastric resection.

A farmer forty-four years old suffered a severe hemorrhage, with collapse and shock, while he was working sixteen and eighteen hours during the wheat thrashing season.

It would seem likely that in many cases this type of hemorrhage does occur during the so-called busy season of the individual's particular business. Occasionally, an infection of the upper part of the respiratory tract is thought to initiate bleeding, or sometimes the ingestion of a large meal of coarse food may be the immediate factor. In some instances exacerbation of symptoms occurs prior to the onset of bleeding.

Other Causes of Hemorrhage—If there is a history of duodenal ulcer, the diagnosis is relatively easy, but there are several other conditions in which hemorrhage is prevalent, and these always should be borne in mind. The most common ones are gastric carcinoma, acute ulcer, erosion and gastritis of all types, esophageal and gastric varices, and benign tumors of the stomach and small intestine. Other less common causes are purpura, splenic anemia, Banti's syndrome, hemophilia, mesenteric thrombosis, lesions of the esophagus, ulcerative colitis, malignant lesions of the colon, bleeding hemorrhoids, severe infectious diseases and vitamin deficiency states, especially when deficiency of vitamin K is involved. It should also be mentioned that in some cases the condition will be obscure. Jenkelson reported it was not possible to find the cause in 9 per cent of 685 cases of bleeding from the upper part of the digestive tract.

Symptoms—We should be reminded again that by the term "hematemesis" is meant the vomiting of gross blood, and that the term "melena" is used to denote the passage of tarry stools. The lesion which is producing hematemesis generally is situated in or above the duodenum, and the lesion which is producing melena probably is located above the midpoint of the small intestine. Bleeding below this point usually is evidenced by red blood in the stool. The effusion of about 60 c.c. of blood into the intestine will produce melena. Usually, about 350 c.c. of blood is required to produce symptoms in the average patient.

The first symptoms of a bleeding duodenal ulcer may be sudden weakness or faintness, immediate hematemesis may or may not follow. Within a short time there may be a desire to defecate. If enough time has elapsed, the stool may be tarry. Syncope may follow defecation. If bleeding persists, shock may ensue. To the many physicians who saw

patients suffering from gross hemorrhage in the recent war, the picture of shock is still vivid in their minds. The pale face, wrinkled blue lips, clouded sensorium, anxiety, speedy pulse and falling blood pressure are all signs of danger. They constitute a warning that some

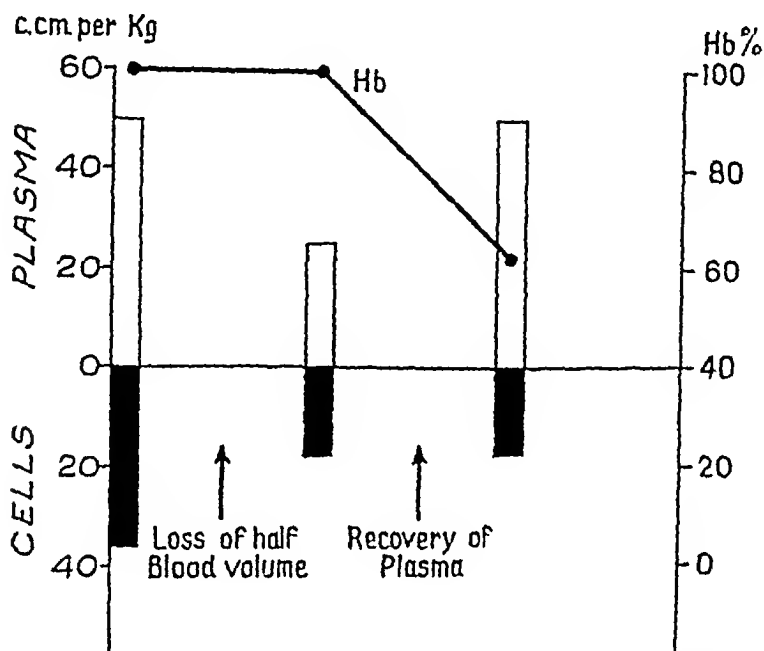


Fig. 160—Schematic representation of how the decrease in hemoglobin after severe hemorrhage is dependent on restoration of plasma volume. The left hand column represents the total amount of blood in the normal human body. The middle column represents what would occur if half the total amount of blood in the normal human body were lost: the value for hemoglobin would remain the same, as seen above the tops of the first and middle columns. In the next few hours the plasma is restored, and the condition depicted in the third column obtains, that is, the volume of erythrocytes remains low, whereas the volume of plasma has returned to normal. A patient whose condition is represented by the third column probably is much better, physiologically, than he would be in the preceding states, yet his hemoglobin is sharply reduced. (Reproduced by permission of the publishers, from Bennet, T. I., Dow, J., Lander, F. P. L. and Winkler, S. Severe haemorrhage from the stomach and duodenum. *Lancet* 2:651-655 [Sept 17] 1938.)

thing must be done rapidly. Shock caused by hemorrhage can be a rapidly fatal condition, and it should be treated early and vigorously.

During sudden hemorrhage there is a loss of whole blood. This will lower the blood volume, but during this stage the values for erythrocytes and hemoglobin are unchanged. This serves to emphasize

the need for repeated observation of a patient in order to determine clinically whether or not shock will ensue. The values for erythrocytes and hemoglobin recede only after the remaining blood calls for more fluid from the tissues, thus diluting the remaining erythrocytes and plasma (fig 160). Studies of blood volume are the only accurate methods for the early determination of the amount of blood lost. Probably such studies are not carried out often enough, in many instances. The infusion of plasma and fluids may be indicated, but experience obtained during the recent war showed that there were no substitutes for whole blood in severe hemorrhage. However, in recent months, the incidence of homologous serum jaundice has served to caution physicians against the indiscriminate use of blood and plasma. The occurrence of this type of jaundice will be an ever-important factor in the future. The danger associated with the use of plasma is infinitely greater. It is extremely hazardous, for instance, to use blood from present or discharged service personnel. If possible, blood which is used should be obtained from one donor only. Slight leukocytosis, and later, an increased number of reticulocytes and nucleated erythrocytes, may accompany the hemorrhage.

Biochemical Changes in Hemorrhage—It has been recognized that massive gastro-intestinal hemorrhage will be accompanied by an elevated value for blood urea. What is the mechanism of this elevation? Two ideas are extant, both of which probably are correct in some respects. The first belief is that when effused blood is present in the intestinal tract, some of it is absorbed in the same manner as are food-stuffs, hence, after the breakdown of these substances, an elevated value for urea results. The other belief is that during the acute phase of the hemorrhage, dehydration and shock may alter renal function to such an extent that urea is not excreted properly. Experimental work has definitely shown that an elevated value for urea can be caused by ingested blood, but to what degree is such elevation brought about in this manner? Clausen in 1938 administered 500 to 600 c c of ox blood to two patients, both of whom previously had had elevated values for urea, resulting from hemorrhage. The first patient had hematemesis, after which the value for urea increased to 70 mg per 100 c c of blood. After this value had returned to normal, he received the afore-mentioned quantity of blood. In eight hours the value for urea was 45 mg per 100 c c of blood. It returned to 36 mg per 100 c c of blood within forty-eight hours. The second patient had melanic stools for sixteen days. Early in the course of the condition the value for urea was 49 mg per 100 c c of blood, and rapidly returned to normal within four to five days. After she received the ox blood, the value for urea increased to 50 mg per 100 c c of blood in eight hours, and returned to 34 mg in twenty-four hours.

These two cases bring up several points. In the first case there was

an elevated value for urea associated with hematemesis. Some writers have said there is no increase in urea after hematemesis only, but of course it is not possible to be sure that in the first case some was not absorbed. In the second case a return of the content of urea to normal occurred in about four days, but melena continued for sixteen days. Both cases show that an elevation of blood urea occurred after the ingestion of 500 to 600 c.c. of ox blood, but in neither case did the value increase to more than 50 mg. of blood.

Possibly, then, it might be inferred that, when there is an increase in urea to more than 100 mg. per 100 c.c. of blood, there must be an additional factor. Even though in many cases the amount of blood lost by hemorrhage is much more than 0.5 liter, it is difficult to be certain that all of the urea elevation is due to absorption. This blood often is rapidly passed, so that there is very little time for absorption. During shock there is a decrease in normal intestinal function. It has been shown that in these cases of hemorrhage there is no alteration in the carbon dioxide combining power or in the blood chlorides. This rules out the direct effect of alkalosis as a factor producing damage to the kidney. In such cases there is a decrease in chloride in the urine, which suggests decreased renal function.

Some writers have said that the clearance of urea is normal in some cases of hemorrhage of the type in question.

Wright, however, giving the details of a case of severe duodenal hemorrhage in which the blood volume was lowered to 4 l. liters, noted that glomerular filtration was only 25 c.c. and the renal plasma flow 70 c.c. per minute. After the transfusion of 850 c.c. of blood, the blood volume increased to 5.4 liters, glomerular filtration was 55 c.c. and renal plasma flow 170 c.c. per minute. After recovery of the patient these values were 90 and 910 c.c., respectively. Wright thought the reasons for such a situation are lowered arterial blood pressure and marked renal vasoconstriction. It certainly seems that in Wright's case decreased renal excretion of urea would be a very important factor in the increase of the urea to 100 mg. per 100 c.c. of blood.

Morlock has observed that a highly elevated value for urea in the blood in the presence of gastric hemorrhage is most often accompanied by severe shock (fig. 161). It seems likely, then, that both absorption of blood as an extrarenal factor and shock causing a renal factor are responsible for the azotemia which occurs in hemorrhage. Since the two factors of absorption of blood and shock are coexistent, they are almost impossible to separate. Of course, it should be mentioned that azotemia will be increased by alkalosis arising from coexistent pyloric stenosis or pre-existent renal insufficiency. It should be emphasized that a high value for urea in the blood may be present in gastric intestinal hemorrhage, but this value will return to normal after bleeding has ceased.

Repeated determination of the value for urea in the blood has been advocated as constituting a valuable diagnostic help. As a rule, a consistently elevated value for urea of 100 mg or more per 100 c.c. of

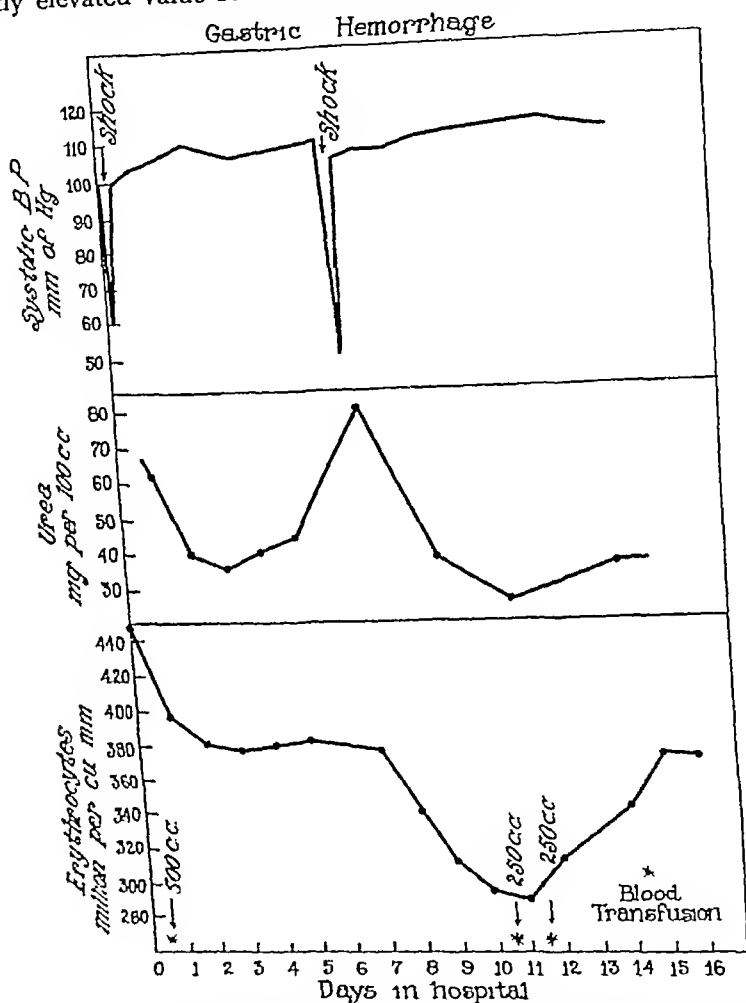


Fig 161—Elevation of the concentration of urea in the blood as the result of massive hemorrhage (Reproduced with permission of the publishers, from Eusterman, G B Peptic ulcer In Nelson Loose-leaf Medicine New York, Thomas Nelson & Sons, 1946, pp 239-266A)

blood points to an uncertain course. Some believe that a consistently elevated value for urea is due to continued hemorrhage, this may be true in many cases, but cannot be interpreted too strictly. Bockus has stated that determination of the content of urea in the blood cer-

tainly is valuable in appraisal of the problem of hemorrhage in many cases

Often there will be a low value for the plasma proteins, because of loss of blood. In other cases there may be an elevation of the bilirubin content of the blood and the urobilinogen content of the urine. The causes for this are not exactly clear. Fever may follow hemorrhage, indicating manifestations of toxicity.

Prognostic Considerations—When the physician is confronted with a patient who has a bleeding duodenal ulcer, a factor which at once comes to mind is the estimation of the gravity of the hemorrhages. How is he to treat the patient? Will the bleeding cease? Is surgical operation indicated?

It is not the purpose of this paper to mention treatment, but we should, nonetheless, like to present the consensus concerning a few points so that some attention to these problems may be stimulated. A bleeding duodenal ulcer will terminate in death in between 1 and 10 per cent of cases. In recent writings the so-called feeding treatment is highly favored in place of the so-called fasting program. The modified Sippy diet is preferred to the Meulengracht regime.

At surgery three things can be done. First, gastric resection can be performed, second, gastro-enterostomy can be carried out, third, ligation or excision of the bleeding portion can be done. Gastric resection is preferable, but bleeding in the duodenum may be very difficult to control during gastric resection. Gastro-enterostomy may not stop the immediate hemorrhage, nor does it prevent recurrent bleeding. Ligation of the bleeding region, especially if the bleeding is due to large erosive lesions involving either of the pancreaticoduodenal arteries, may be extremely difficult or impossible. In the surgical treatment of the patient who has hemorrhage the mortality rate is very high, between 20 and 30 per cent. The mortality rate is certainly lower, possibly around 5 per cent, among such patients if they are operated on within the first twenty-four hours, but since in more than 90 per cent of cases hemorrhage ceases spontaneously, early surgical intervention cannot be advised. Miller has said, "Massive hemorrhage is a medical problem—acute perforation is a surgical one." The role of vagotomy in the treatment of bleeding duodenal ulcers is yet to be determined. It may prove to be beneficial in the prevention of recurrent hemorrhage, but it seems unlikely to be of value in the acute phase of bleeding.

Perforation Caused by Duodenal Ulcer—Acute Perforation—Acute perforation of a duodenal ulcer is the most dreaded of all complications. It is accompanied by the highest mortality rate of three complicating entities, which are in the order named, acute perforation, hemorrhage and pyloric stenosis. It is an exigency which demands immediate diagnosis and surgical intervention. If the patient is oper-

ated on within the first four to six hours, the outlook is good, but after eight hours the mortality rate rapidly rises to between 50 and 70 per cent. It is the purpose of this paper to point out the importance of early recognition and prompt surgical intervention, since the internist and general practitioner usually first see these emergencies. The first physician who sees these patients should be familiar with the early features of the conditions, since by the time the surgeon sees the patient, certain aspects may be changed and obscure the situation. Elhason and Ebeling, as quoted by Bockus, in a series of records collected in 1940, gave the mortality rate as 25 per cent, after operation.

INCIDENCE—Determination of the actual incidence of perforation in duodenal ulcers is not an easy task. The figure will vary in relation to the type of cases studied, geographic location of patients and accuracy of diagnosis. It is readily seen that many patients with ulcers do not come under the cognizance of the physician, and many ulcers that are encountered will not be reported in a given survey. Figures based on duodenal ulcers seen in an outpatient clinic will differ from figures concerning a group of patients who are treated in a hospital. The percentage of perforating ulcers encountered in a large charity hospital will be different from the percentage of those encountered at the Clinic, for instance, to which many patients come during the quiescent phase of their ulcer. Some ulcers will seal spontaneously, others of the subacute type will not be diagnosed, nor will they be treated surgically. In some cases, at operation, it will be difficult to determine on which side of the pylorus the lesion is located.

Most authorities agree that perforation is more common in gastric ulcers than in duodenal ulcers. This brings up the question of the actual incidence of gastric ulcers in relation to duodenal ulcers. We have referred to this figure as being 1:13 at the Clinic. This figure is at variance with a report from Stockholm between 1930 and 1940 by Ilre and Muller, who said that the incidence of gastric ulcers in relation to duodenal ulcers was 1:35. The actual incidence of perforating gastric ulcers in relation to perforating duodenal ulcers was given by Williams and Walsh as 1:4. There seems to be a great disproportion between the incidence of acute perforation in men and women. Figures in this respect vary between 25:1 and 47:1.

Eusterman said that in the majority of cases perforation is spontaneous, but such factors as unusual physical exertion, trauma to the body in the form of direct blows, falls or vigorous massage of the abdomen, may cause the ulcer to rupture. Palpation of the abdomen during roentgenoscopic manipulation has, in a few instances, precipitated perforation. Often, perforation may occur after a large meal. Acute perforation when the stomach is filled is accompanied by an infinitely higher mortality rate than is perforation occurring when the

stomach is empty. The incidence of acute perforation in relation to the number of duodenal ulcers coming under the surveillance of a physician probably is in the neighborhood of 5 per cent.

ANATOMIC FEATURES—In most cases, free perforation takes place on the anterior wall of the duodenum. Perforation usually is small, being less than 0.5 cm. in diameter. Many perforations are almost pin point in size, and are hard to find. Often they have already closed by the time surgical operation begins. Usually, perforating gastric ulcers are larger than perforating duodenal ulcers. This could be due to the greater frequency with which a crater forms in gastric ulcer, and the action of the unbuffered acid gastric juice in such lesions. Balfour, however, said that in the case of gastric ulcer closure can be effected with more freedom than can closure after excision of duodenal ulcer, since the problem of deformity resulting from closure is not presented. It can be seen readily that lesions on the anterior surface of the duodenum usually do not have a protective covering, so that the likelihood of the sudden occurrence of symptoms and generalized contamination of the peritoneal cavity is very great. It should be remembered that the duodenum actually is a retroperitoneal structure, being covered anteriorly by a thin layer of visceral peritoneum, but posteriorly it is contiguous to retroperitoneal tissues and the pancreas. The inferior border of the first portion of the duodenum is in direct contact with the pancreas, and the superior border is partly enclosed by the right lateral edge of the lesser omentum. When the lesion opens into these areas, the common terminology usually has been "chronic perforation." Probably "chronic perforation" actually is acute perforation when it occurs in that area of the duodenum in which, as noted previously, it is covered by protecting tissues, so that the contents thus do not spill freely. One of us (Rivers) has pointed out the features and importance of these penetrating lesions in a previous publication.

SYMPTOMS—The symptoms of this acute accident have been described by many writers, but the description by Movniliin probably is unexcelled. We feel this is such a classic that it should be repeated herein.

The agony suffered by the patient is almost beyond belief, and is written on every line of a face that speaks of torture. The face is pale, haggard, anxious and appealing, the eyes wide and watchful, the brow and temples bathed in sweat, the hair soaked. The patient struggles for breath in short, panting respirations which are wholly costal, for the diaphragm, being an abdominal muscle, is fixed. Words spoken are jerked out in expiration only, every syllable is part of a deep moan. What strikes every onlooker is that the patient's body is rigid and motionless, no slightest movement dare be attempted. If an endeavor is made to move the abdomen, the patient's hands are at once lifted in protest and in protection, but the chest and abdomen stay motionless. When examination is made it is realized at once that the patient is cold, and the temperature will rarely be found more than 95° or 98° F. The abdomen is immobile and the muscles are taut and rigid. "Hard as a board," it is said, but if there is anything harder it is

the abdomen in this time of catastrophe. A further examination of the abdomen will almost always show an area of greater tenderness, and, if possible, of added rigidity over the area involved in stomach or duodenum. The pulse is normal, blood pressure is not diminished.

It might be said that this early period of prostration can be called the "chemical" phase, because of the severe reaction caused by the pain set up by irritation of the very sensitive nerves in the parietal peritoneum by acid gastric and duodenal contents. Later, as Moynihan wrote, there is an intermediate stage in which the pain subsides. This may be the result of actual necrosis of the nerve endings, and may be analogous to the subsidence of pain in coronary occlusion within a few hours because of destruction of the afferent pain fibers in the lesion. In this middle stage the diagnosis may be more puzzling. But this middle stage is followed by a stage in which the pulse quickens, the temperature starts to increase, the abdomen begins to distend and the picture gradually becomes one of a septic condition. This can be called the "bacterial" phase, since infection arising from contamination is present. Summarizing, we can say that (1) the acute chemical, (2) the intermediate and (3) the peritonitic stages often can be recognized.

Morley has stressed the importance of shoulder-tip pain. He explained this as being initiated by irritation of the central part of the diaphragm, which is innervated by the phrenic nerve, coming from the third and fourth cervical segments. Since the shoulder tip and the diaphragm are subserved by the same spinal segment, the pain from the peritoneal side of the diaphragm may be interpreted as coming from the area of the shoulder. Bockus said that shoulder-tip pain may be felt in a third to a half of cases. This pain may arise early, later to be obscured in the sensorium by the development of more severe abdominal pain. Morley presented the interesting point that after spinal anesthesia shoulder-tip pain again may be felt, he pointed out the nature of its origin and the method of interpretation. He also said that in ruptured ectopic pregnancy shoulder-tip pain may be due to central diaphragmatic involvement. He presented this as the basis for his belief that the parietal peritoneum is highly sensitive, and that pain may be caused by sterile chemical contents. Often, there is widespread extension of pain into the lower part of the thorax and back, in addition to the abdominal situation. The sudden onset and epigastric or upper abdominal location of pain are the most characteristic features. Generally, vomiting is not a feature, since any violent diaphragmatic movement is accompanied by intense pain.

DIAGNOSIS—The clinical picture of a patient with a previous history of duodenal ulcer, and a seizure of sudden agonizing pain with board-like rigidity in the upper part of the abdomen will, in the majority of instances, make the diagnosis. However, in 15 to 25 per cent of cases

there is no previous history of ulcer, and the observations may not be clear-cut. The suddenness and severity of the onset are important in recognition. The boardlike rigidity usually noted to begin in the upper third part of the abdomen spreads gradually downward. As a rule it proceeds first to the right side because of spillage over the colon and gravitation to the right iliac fossa. Later, the entire abdomen becomes rigid. At auscultation the abdomen is usually quiet. The patient is motionless in contradistinction to the patient who has colicky visceral pain. Rectal examination always should be carried out. Tenderness in the cul-de-sac of Douglas or the rectovesical pouch usually accompanies peritonitis. Tenderness on palpation of a mass in the right iliac fossa usually would point to an appendiceal abscess. Palpation of nodular, hard, fixed masses in the midline above the prostate gland would indicate carcinomatous implants. Occasionally, this may be the only positive physical observation in gastric carcinoma, the presence of which would point to that as the cause of perforation.

The finding of free air under the diaphragm is one of the most important of the confirmatory findings. This frequently points to the positive diagnosis of a ruptured gastric or duodenal ulcer. The erect or the sitting positions are the best in which to place the patient to demonstrate pneumoperitoneum in the roentgenogram. Of the lateral positions, the best probably is that in which the patient's right side is up, since air present above the liver usually is seen more distinctly when the body is thus placed. Air in the stomach, colon and lungs should not be confused with free air in the abdominal cavity. Failure to elicit hepatic dullness at percussion is due to the aforementioned conditions. The presence of leukocytosis is helpful to the diagnosis, but it is by no means always present.

DIFFERENTIAL DIAGNOSIS AND PERFORATION OF DUODENAL ULCER.—The diseases which should be considered in diagnosis are acute pancreatitis, perforating gallbladder, perforating appendix, mesenteric embolism and thrombosis, coronary occlusion, acute intestinal obstruction, biliary tract colic, renal colic, diverticulosis of the transverse colon, acute diaphragmatic pleurisy, crises of ulcer, visceral crises of tabes dorsalis, ruptured extra-uterine pregnancy, pyelophlebitis, acute perieriditis, carcinoma of the stomach and pancreas, ruptured abdominal aorta and ileus due to injuries of the spinal cord.

Acute Pancreatitis.—Acute pancreatitis probably is the disease most likely to simulate perforation of a duodenal ulcer. In both conditions there may be severe agonizing pain, located in the epigastrium and across the upper part of the abdomen. The hypodermic injection of morphine may not greatly affect the pain of either entity. Generally, however, perforation of an ulcer is followed by the onset of boardlike rigidity of the upper part of the abdomen which does not b

diseases than any other childhood tumor except, perhaps, intracranial neoplasms. Although lymphosarcoma has been considered by some authors to be one of the most common varieties of children's tumor, we have not observed large numbers of this tumor in children at Memorial Hospital. This may be attributed to the fact that many cases which are initially considered to be lymphosarcoma later show evidence of acute leukemia.

Lymphosarcoma must be differentiated from other causes of lymph node enlargement, swellings (e.g., hypertrophy of a tonsil), intrathoracic, intra-abdominal and retroperitoneal masses.

The symptoms in some cases of lymphosarcoma may be fulminating.

TREATMENT—If a primary site for the tumor can be found, aggressive treatment should be directed to it. If the lesion appears operable, surgery should be elected as the method of choice. If the surgical problem is too involved, irradiation should be tried. These cancers usually carry an unfavorable prognosis. However, one of the children in the Children's Tumor Registry series, a girl of 11, who had a lymphosarcoma of the cervical nodes with no detectable primary site in the pharynx or oral cavity, has survived six years, following a radical neck dissection.

Unfortunately, metastasis may occur before the case comes under observation. Treatment in such instances is palliative and roentgen therapy is the preferred method.

Hodgkin's Disease—This does not occur frequently in children but several new cases are seen annually at Memorial Hospital. It is well known that this disease is more common in the male than in the female patient.

Being a lymphogranuloma, Hodgkin's disease presents diagnostic difficulties which at times are as great as those of lymphosarcoma. The symptoms and signs are weakness, itching, lymph node enlargement, and, occasionally, fever or pallor. Generally, the enlarged nodes are evident externally or by roentgenographic examination and these findings will aid in the diagnosis. The nodes are usually large, forming a collar about the neck or bulky masses in the axilla and inguinal region. Early in the course of the disease the nodes may be indistinguishable, except by biopsy study, from any other syndrome presenting lymph node enlargement. The spleen and liver may not be enlarged. The lungs are not infrequently affected and diffuse infiltration is often seen on x-ray examination, in addition to a mediastinal or tracheobronchial mass.

Hodgkin's disease is to be differentiated from conditions causing lymph node enlargement, such as tuberculosis, leukemia, lymphosarcoma and neuroblastoma, as well as intrathoracic and intra-abdominal growths.

TREATMENT—The treatment is palliative. Therapy is preferably by

pancreatitis Comfort, Gambill and Baggenstoss, in an analysis of symptoms in twenty-nine cases of chronic relapsing pancreatitis, found that definite rigidity was not mentioned in a single record. Often, however, muscle spasm and deep tenderness were reported. They found that the ratio of occurrence of these symptoms, computed according to sex of patients, was 6.2 1, in favor of males. We mentioned earlier the report that the ratio of the incidence of perforating ulcer, computed according to sex of patients, is more than 25 1, in favor of males. Gambill believes that the pain of acute pancreatitis is often gradual in onset, and that it may increase to a peak within a few hours, often persisting for several days, and then gradually subside. It should be mentioned, also, that the pain of acute pancreatitis may have an irregular course.

This is somewhat different from the abrupt onset of the severe pain accompanying perforation of a duodenal ulcer, but occasionally in pancreatitis there is a short onset. Comfort and associates stated that the picture in acute pancreatitis is one of repeated seizures of pain, in their cases the average period from onset to diagnosis was 48 hours. This course may resemble somewhat that of chronic perforating duodenal ulcers, but repeated acute perforations are rare. In a series of twenty-nine cases of chronic relapsing pancreatitis reported by Comfort and associates, they noted an elevated value for bilirubin in 38 per cent of cases, glycosuria in 34 per cent, and diabetes of varying degrees in 24 per cent. They found retention of dye in seven of fifteen cases in which the bromsulfalein test of hepatic function had been done. In eight cases serum amylase was computed during seizures of pain, and was found to be elevated in four of these eight. This bears out the impression that determination of serum amylase may not always be helpful in the making of the diagnosis. Comfort and associates found the values for serum lipase to be elevated in about the same percentage of cases as those in which the serum amylase was increased. It should be borne in mind that cholecystic disease is a precursor of acute pancreatitis in a high percentage of cases.

Acute Perforation of the Gallbladder—A history of cholelithiasis in females, obesity, a long history of qualitative dyspepsia, jaundice and a history of biliary colic are factors which point to cholecystic disease. Eusterman said that acute perforation of the gallbladder often occurs after the apparent subsidence of an attack of cholecystitis. The recognition of this feature can be very helpful. Tenderness and rigidity usually are confined to the right upper abdominal quadrant, since there is a strong tendency toward localization in this type of perforation. Emergency surgical treatment also is usually indicated.

Acute Appendicitis and Perforation—Occasionally, inflammation of a high lying appendix—at times situated as high as the normal position

of the hepatic flexure—may cause some confusion in diagnosis. Rupture of an appendiceal abscess in the right iliac fossa may follow the right gutter upward in some instances. In a considerable number of patients the early pain of appendicitis may be periumbilical, but the pain will be diffuse, dull and ill-localized in distinction to the sudden, sharp pain of a perforating duodenal ulcer. Usually, in appendicitis, the pain, tenderness and rigidity, pretty much confined to the right lower abdominal quadrant, make the diagnosis. When a patient has pain of undetermined nature, the abdomen should be explored through a right rectus incision to allow free inspection of both the appendix and the duodenum. Pneumoperitoneum rarely, if ever, occurs in rupture of a viscus situated below the duodenum.

Mesenteric Embolism or Thrombosis—This is a disease to be suspected when there is evidence of embolism or thrombosis elsewhere, and when a systemic or abdominal infectious disease is present. Often there is cardiovascular disease, such as mitral stenosis, coronary occlusion, arteriosclerosis, hypertension or periarteritis nodosa. Generally, the signs of obstruction, with distention rather than rigidity, are evident. The pain may not be severe, it may be located in the midabdominal region or it may be diffuse. Bloody diarrhea may occur. Roentgenograms of the abdomen as a rule show small intestinal obstruction without pneumoperitoneum.

Coronary Thrombosis—Usually, there is a sudden onset of severe pain in myocardial infarction, and this pain often is located at the xiphisternum or midsternal area. There may be some pain and muscle spasm over the upper part of the abdomen, but boardlike rigidity of the abdomen does not occur. The pain of coronary occlusion may extend to the left shoulder and down the inside of the left arm, but it can also extend to both shoulders, both arms and to anterior neck areas. It can be widespread over the anterior part of the thorax. In many cases there will be a history of angina pectoris, in some there may have been a previous infarction. An emergency electrocardiogram should be made. More and more clinicians are depending on electrocardiographic evidence in the diagnosis of myocardial infarction. Infarction detected by means of the electrocardiographic findings usually is classified as being situated on either the anterior or posterior wall (fig 162). Early anterior infarction is diagnosed in lead I and in the precordial leads. The changes are similar in that there is an elevation of the ST junction. There may be a Q wave, which is more likely to occur in the precordial leads than in lead I. In infarction of the posterior wall there may be changes only in lead III. These again are elevation of the ST junction and most often an initial Q wave. When precordial leads are altered, which occurs in about 60 per cent of lesions of the posterior wall, depression of the ST segments generally is noted.

Acute Intestinal Obstruction—Often, in the presence of this entity, there is a history of previous episodes of obstruction. Other abdominal diseases may be known to be present. Most likely the patient previously has undergone abdominal surgery, and has several scars in evi-

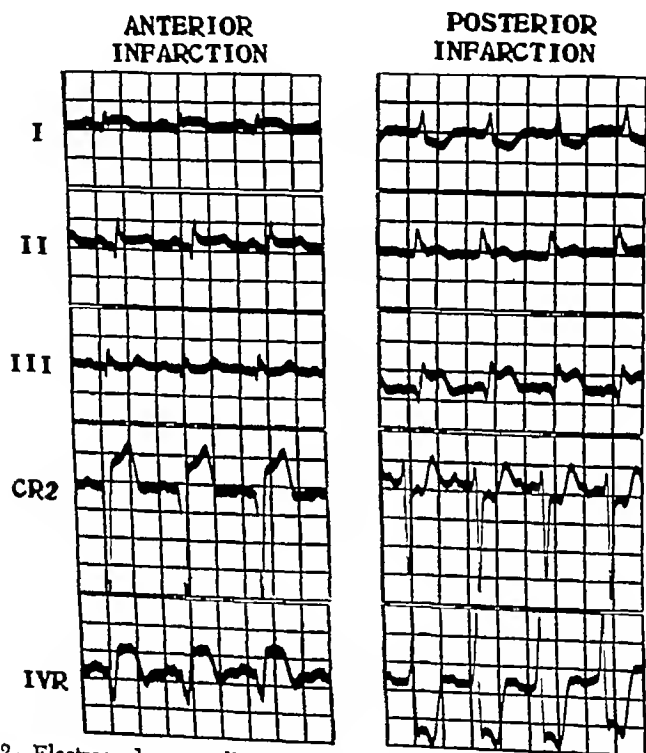


Fig. 162—Electrocardiogram illustrating acute anterior infarction and acute posterior infarction

dence. As a rule, there is abdominal distention without rigidity. Protracted vomiting is a feature, with marked disturbance in blood chlorides. The abdomen conveys the picture of intense intestinal activity, rather than the quietude which characterizes acute perforation with peritonitis. The pain has a tendency to be colicky in nature, and when the obstruction is situated low, bloody stools may be passed. Roentgenograms of the abdomen will disclose distention of the small bowel, without pneumoperitoneum.

Colic of the Biliary Tract—This rarely presents a problem, but the location of pain and the sudden onset may resemble the acute per-

foration of an ulcer. The pain of this type of colic, however, usually remains localized over a small area just below the xiphoid process, and often extends through to the back. The patient is restless, and moves about trying to find a position of relief, whereas the patient who has a perforated ulcer is quiet. There may be a history of colic which could be relieved with opiates, or evidence of calculi in a plain roentgenogram of the abdomen. Often, there are hyperbilirubinemia and bilirubinuria. These are rarely found in the presence of perforating ulcers.

Renal Colic—This generally presents little difficulty, for the pain most often is unilateral and extends downward, to follow the distribution of the first lumbar segment, as suggested by Lewis, into the inguinal areas or the scrotum. The pain is colicky in nature, the patient is restless, and opiates usually relieve the distress. There may be a history of previous renal calculi or evidence of them in the roentgenogram. Hematuria and pyuria may be present. Rigidity and shock do not accompany the so-called colic type of entities.

Perforation of a Diverticulum of the Transverse Colon—Occasionally, this disease will present a picture somewhat similar to that of an acute perforating ulcer. More often, however, the picture will resemble that of a ruptured gallbladder or a subacute perforating ulcer. The diverticulum may have been found during a previous roentgenologic examination made with the aid of a barium enema. Inflammation usually is exacerbated by constipation. The following case is an example.

A white man forty-eight years old came to the Clinic because of symptoms of obstruction of the urine. Before any investigation was instituted, the patient experienced a sudden attack of moderate pain, with tenderness and rigidity that were maximal to the right of, and above, the umbilicus. There was no history of gastro-intestinal disease. Surgical intervention revealed several subacute, perforated diverticula in the right half of the transverse colon without actual rupture or peritonitis, and an extreme degree of tenderness.

Subacute Perforating Duodenal Ulcer.—This term is reserved to denote those lesions which may perforate gradually or suddenly to a small extent into the free peritoneal cavity, but which are quickly walled off by various tissues and organs. They may momentarily resemble an acute perforated ulcer, but do not ordinarily proceed to the catastrophic state. By chronic perforation is usually meant penetrating, erosive lesions into the tissues surrounding and posterior to the duodenum, but lesions which do not involve the free peritoneal cavity.

Subacute perforation of a duodenal ulcer may be sudden, but the consequent peritonitis is localized, and no free fluid, or only a minimal

amount, may exude from the aperture in the duodenal wall. In the case which we shall report in this section minute bubbles of air were seen to come through the small hole in the wall of the bowel.

Several reasons can be given to explain the failure of the duodenal contents to spill unimpededly through the ruptured area into the abdominal cavity in subacute perforating duodenal ulcer. In the first place, the aperture may be extremely small, so that inflammatory reactions about this area may seal it off. Generally, the ulcerating progress of the lesion is slow, so that the wall of the bowel has already become partially sealed to some neighboring organ or to some ligamentous attachment. This would impede and entangle the slowly escaping contents of the bowel long enough for the consequent tissue reactions to plug the hole. Another factor which must be important is the fortuitous one that rupture occurs when the intraduodenal pressure is low or when no food content happens to be present. A case in point will be presented.

A man fifty-nine years old presented himself at the Clinic because of indigestion. He said that for three years he had had periodic episodes of epigastric distress which would persist for a short period. He was able to secure relief by taking milk of magnesia and by belching. Ingestion of food had not adequately relieved him during the preceding few months. There had been some loss of strength and an increase in the severity of his distress until four days before we saw him, at which time he had noticed tarry stools. He noticed that he perspired very easily. While he was at the Clinic he vomited large amounts of dark, blood-stained material. He had some degree of localized pain in the upper right abdominal quadrant, and marked tenderness in this area. There was some evidence of irritation, as manifested by rigidity and an extreme degree of tenderness.

Estimation of gastric acidity showed values of 54 units for total acidity and 38 units for free hydrochloric acid (method of Topfer). Material aspirated from the stomach amounted to 200 c.c. A roentgenogram showed a duodenal ulcer, with some evidence of obstruction.

At operation subacute perforation was found to have occurred on the inferior margin of the duodenal ulcer, the perforation began $\frac{3}{2}$ inch below the pylorus and extended three fourths of the distance across the duodenum, from below upward. Small bubbles were seen to emerge from the site of perforation.

It is important to recognize subacute perforated duodenal ulcer preoperatively because the methods of therapy are different from those instituted in the case of acute or chronic perforation of a duodenal ulcer.

The symptoms of subacute perforation are very similar to those of acute perforation except that in the former condition the pain is less acute and widespread, and there are no systemic reactions, as there are in general peritonitis. For several days prior to actual perforation there may be intensification of the symptoms generally, and a localizing area of pain and tenderness may develop. Then, suddenly, excru-

ciating pain develops, usually to the right of, and slightly above, the umbilicus. Movement or jarring or touching of this area increases the severe pain. The patient lies quietly in bed, afraid to move because to do so will intensify the pain.

If food is withheld and the patient is kept very quiet for twenty-four to forty-eight hours, the process usually becomes walled off, and the acute symptoms disappear. Marked tenderness and muscular rigidity surrounding the area of perforation persist, frequently an inflammatory mass also persists. This mass gradually may subside and ultimately may disappear. At times an abscess forms in the region of perforation. At other times, the localized signs of a walled-off perforation rapidly give way to those of the catastrophe of acute perforation, although this event is rare. If it does happen, the excruciatingly severe pain then recurs, it becomes wider in distribution and the abdomen becomes boardlike.

Chronic Perforating Duodenal Ulcer—This term is used to denote those lesions which have perforated through the wall of the duodenum into contiguous tissues, but not freely into the peritoneal cavity. We should like to use the term "penetrating" to denote those lesions which have burrowed deep into the duodenal wall, but which have not extended through the serosa.

In the past, it has been recognized and written by others that there is simply a "change" of symptoms after a lesion has become chronically perforated. We believe, however, that previously many details and important aspects have been overlooked in study of these cases, and that in many instances the true condition has been confused with disease of other organs. Recently, we carefully studied a number of these patients, and we have come to some conclusions which we believe are of importance in the analysis of these cases.

The basis for interpretation of these chronic perforating lesions is in the study of the pain behavior, and this is influenced by the extra duodenal tissues which are invaded. It is well recognized that the uncomplicated duodenal ulcer sets up pain impulses which are carried by the visceral afferent nerves. We know that pain carried over the visceral afferent nerves is more mild, ill-defined, somewhat illusive, poorly localizable, and is different from the more sharp, severe localizable type of pain that is carried over somatic nerves. As long as the lesion remains confined to the duodenal wall, the symptoms usually are typical of an uncomplicated ulcer. But when this ulcer becomes perforated and involves tissues adjacent to it, an entirely different type of symptom complex arises. The pain becomes more severe, and there is a shift in the location of pain. The reason for this different type of picture is probably that at this time, after the lesion has perforated, it involves tissues supplied by somatic sensory nerves which are be-

heaved to have a much greater sensitivity and localizing power than visceral afferent nerves

The over-all picture of the symptoms of perforating ulcer thus is due to an interaction of the two syndromes, one originating within the viscus, the other in somatic structures. The tissues most commonly involved in these perforating lesions are the pancreas, the lesser omentum (which may be divided into the hepatogastric and hepatoduodenal ligaments) and the mesocolon. These structures contain somatic sensory nerves which interpret pain in a different way than do the nerves picking up impulses from the bowel. Therefore, it is easily seen that there will be a new group of symptoms caused by involvement of these organs. Because of the fact that these organs have a different nerve supply, it may be possible, in perhaps as high as 90 per cent of cases, clinically to determine accurately on the basis of interpretation of pain the organ which has been invaded by the chronic perforating duodenal ulcer. There is a diagnostic key in the location and extension of this secondary pain, because the pain is interpreted as being felt in the peripheral distribution of the nerves occupying the same segments which were invaded in their peritoneal distribution by the inflammatory products of penetrating or perforating ulcers.

The organ most commonly invaded by a perforating duodenal ulcer is the pancreas. This is easily understood, since the first and second parts of the duodenum and the pylorus are in such intimate contact with the pancreas. Should the inflammatory process spreading from the ulceration invade the pancreas, the resultant secondary pain usually is felt about the level of the umbilicus, and it extends to either the right or left, with extension through to the back to the region of the upper lumbar vertebrae. If lesser omental tissues are invaded, an occurrence which probably is next most common after invasion of the pancreas, the pain generally is in the epigastrium, and it extends to the right or left lower costal area and to the back, about the midthoracic area. Sometimes, invasion of the pancreas produces pain which extends downward, this pain could be caused by involvement of the mesocolon as it is reflected from its lower margin. Invasion of the mesocolon or the root of the mesentery of the small bowel usually produces a pain that extends downward, occasionally as low as the inguinal area. Involvement of the anterior abdominal wall usually produces a pain the distribution of which closely approximates the area invaded, from which area it may spread laterally and to the back. If the diaphragm is involved, the shift is into cutaneous areas supplied by nerves from the same segment to which the sensory phrenic fibers are distributed.

Thus, this would produce pain in the base of the neck, the supraclavicular area, and the tip of the shoulder on the side on which the phrenic nerve was irritated.

It is not always possible, by study of the extension of pain, to determine with any degree of accuracy which somatic tissues are invaded by the inflammatory reactions of a perforating ulcer. This is understandable when the reflections of the various tissues which constitute the posterior abdominal wall are considered. So long as the pathologic process remains localized to one area in which, for instance, only lesser omental tissues are involved, the pain pattern usually is distinct, with high epigastric extension of pain. The pain needs to extend only a short distance, however, to involve also the pancreas.



Fig. 163—Characteristic positions, often assumed by patients who have a penetrating duodenal ulcer, to obtain relief from pain. *a* and *b*, Positions resorted to in bed; *c*, characteristic leaning-forward position, with hand exerting pressure over the epigastrium.

in which case reference of pain is likely to be lower. In this way, some paradoxical and confusing references of pain may occur. Careful evaluation of these referred pains, however, usually makes fairly accurate diagnosis possible.

So far as the extension of pain into secondary areas is concerned, it makes little difference whether the perforation is gastric, duodenal or jejunal in origin, it depends on the tissues to which the inflammatory process extends. If, as in the case of penetrating ulcer (the ulcer being contained in the visceral wall), the ulcer begins to heal and the inflammatory metabolites cease to irritate these somatic structures, the reference of pain into secondary areas often stops completely, with the visceral syndrome in its pure form re-establishing itself. In the

majority of cases in which the somatic syndrome is initiated, it completely overpowers the visceral syndrome and the early symptoms of the ulcer are replaced by a new syndrome. It is well to mention that, once the pain has been referred into secondary areas, the hope of relief from medical treatment is rather dim. Although some of the patients do respond to medical management, their progress is very slow and in the majority of instances the patient will have to undergo a surgical procedure.

We should like to present a clinical observation concerning this group of patients with perforating duodenal ulcers into surrounding areas, and to mention that this is a very striking feature of the entity. This observation is the fact that many of these patients find that they gain relief from their pain by the adoption of certain postures (fig 163, *a*, *b* and *c*). They may be seen walking around slowly in a bent-over position, leaning toward the right, with their hands pressed tightly against their right upper abdominal quadrant. Jarring may cause acute pain in this area. When lying in bed, the patient may be found curled up on the right side, with the right leg drawn up, or he may lie on the left side with the right leg drawn up over the left leg and pulled close to the body. Occasionally they assume the knee-chest posture, thus obtaining some relief of pain.

DUODENAL ULCER PERFORATING TO THE PANCREAS

A clergyman forty-eight years old presented himself at the Clinic because of hypogastric and epigastric pain. For many years he had experienced periodic indigestion in attacks that would persist one week to three weeks. After these attacks he would be entirely comfortable for as long as a year. The distress, when it occurred, was spread diffusely over the epigastrium and arose several hours after the ingestion of food. The patient found that he could quickly relieve the distress by taking a cracker or some milk or by using an alkali which his physician had given him. Gradually, the attacks became more frequent, the periods of relief became shorter, and the pain became more severe. Pain also commenced to extend toward the upper right abdominal quadrant into the right part of the back, at the level of the ninth or tenth thoracic vertebra. The distress was sharply localized to an area about the size of a dollar and was limited to the right of the spinal column. After this distress had established itself, the symptoms would be less amenable to the usual methods which the patient had employed to secure relief.

For several years the patient continued to experience this type of distress. About two years prior to his visit to the Clinic he had begun to experience a new type of pain. This was a boring, dull, deep-seated, severe distress which was felt in the umbilical area and which extended to the right and left of the midline. This pain extended into the back, at a level lower than that previously experienced, the region of the first and second lumbar vertebrae. The pain was extremely severe, on numerous occasions an opiate was necessary to control it. There were very few days in the six months prior to the patient's visit to the Clinic when he had been completely free of pain and, when relief had occurred, it never had lasted more than one to two days. It was suspected that he was becoming addicted to the use of opium because of his frequent demands for relief by the hypodermic injection of an opiate. He found that he was able to

make himself somewhat more comfortable by getting into a knee-chest position in bed. He also occasionally had resorted to getting down on the floor on his hands and knees.

On arrival at the Clinic, the patient was promptly hospitalized because of the severity of his pain. On a regimen consisting of frequent feedings, and the use of antacids and antispasmodic agents, he was slightly more comfortable, but he continued to have some distress. The use of opiates often was necessary to control this.

Estimation of gastric acidity showed values of 80 units for total acids and 63 units for free hydrochloric acid (method of Töpfer). Roentgenologic examination showed a duodenal ulcer. At operation the patient was found to have an extensive perforating duodenal ulcer, the base of which was in the body of the pancreas. Resection was performed, after which the patient promptly became comfortable. There had been no recurrence of his preoperative complaint to the time of this report.

DUODENAL ULCER PERFORATING TO THE LESSER OMENTUM AND GALLBLADDER

A man fifty-nine years old presented himself for examination because of indigestion. For eighteen years this man had had epigastric pain occurring in attacks which would last several weeks. After these attacks he usually would be free from symptoms for several months. On occasion he had noted the passage of tarry stools. Pain would arise two or three hours after meals, occasionally it would awaken him at night. About ten years after the onset of symptoms he had had a gastric hemorrhage, as manifested by the vomiting of blood and the passing of tarry stools. After that episode, symptoms became more severe, periods of freedom from distress were shorter, and the patient found that relief was obtained by the use of small amounts of food or alkali less adequately than before. Two weeks before coming to the Clinic a new type of pain developed which extended from the epigastrium into the thorax and into the right upper abdominal quadrant. The pain was so severe that it required the use of morphine. A physician who referred him to the Clinic was suspicious that he might have gallstones. Since that time he had had no relief of pain, although occasionally during the day there would be periods in which the pain was not so acute. During the two weeks prior to his coming to the Clinic he had not obtained significant relief by any means except the hypodermic injection of opiates, which had been used frequently. The patient found that he could get some degree of relief by the exertion of pressure over the right upper abdominal quadrant and by bending over. The pain was epigastric, with the usual extension into the thorax and back to the right of the lower thoracic portion of the spinal column. Estimation of gastric acidity showed values of 58 units for total acidity and 46 units for free hydrochloric acid (method of Töpfer). Material aspirated from the stomach amounted to 90 c.c. A roentgenogram of the stomach disclosed a duodenal deformity.

At operation the patient was found to have an ulcer which had resulted in attachment to the gallbladder and liver. Partial gastrectomy was performed.

PERFORATING DUODENAL ULCER WITH PAIN EXTENDING INTO THE LOWER AREA OF THE ABDOMEN

A man fifty years old came to the Clinic because of indigestion. In his late thirties he had begun to notice mild epigastric distress, which would arise two or three hours after meals. He could obtain relief by the use of soda or by taking of small amounts of food. The attacks occurred in episodes which would persist for about ten days or two weeks, after which he would be comfortable for two or three months. These episodes had continued until he was fourteen

irradiation Intensive local treatment is given if an individual site is found, or general body irradiation may be employed if many areas are involved

TUMORS OF THE GENITOURINARY TRACT

The most common malignant tumor of the genitourinary tract is Wilms' tumor (embryonal adenomyosarcoma)

Wilms' Tumor.—This is a tumor of very early life, occurring usually before the fifth year It has been frequently observed in early infancy It is rarely bilateral



Fig 66—Wilms' tumor (E St G, female, aged 4½ years) Left kidney showing the well circumscribed mass usually found in this disease

There are usually no subjective symptoms until the tumor attains a size sufficient to cause intra-abdominal pressure which results in discomfort or actual pain and sometimes in constipation Urinary symptoms, such as hematuria, are rare A mass in either side of the abdomen of a young child should be regarded as a Wilms' tumor until this possibility has been excluded

years old, when they became more severe. He then came to the Clinic. A diagnosis of duodenal ulcer was made, and a medical regimen was outlined for him. For a while he was more comfortable. Then the episodes of indigestion recurred and became more severe. The distress was less tractable to alkalis and food, and the period of relief from symptoms was shorter. At that time the pain, which originally had been epigastric, began to involve the right upper abdominal quadrant as pleural pain does, and it extended to the right part of the back and to the lower thoracic vertebral area.

At the age of forty-three he had a gross gastro-intestinal hemorrhage, after which he vomited blood and passed tarry stools. When he was forty-seven years old he had begun to experience a new type of pain. This pain was hypogastric, and extended to the lower costal area, and from there to the lumbar area. The pain still maintained some of the characteristics that the patient previously had experienced, that is, it occurred two or three hours after meals. Some degree of relief was obtained by the use of soda. One year after his visit to the Clinic he had a severe attack of pain which required the hypodermic injection of opiates and which was localized to the right infracostal area and extended to the right lower abdominal quadrant, occasionally spreading to the right hip and into the right lumbar area. With this, he occasionally experienced epigastric pain two or three hours after ingestion of a meal. Some degree of relief could be obtained by the taking of food and soda. This epigastric syndrome, however, was always rudimentary in importance as compared with the right hypochondriac pain. It was frequently necessary for him to receive an opiate for the right abdominal pain. His physician was beginning to suspect that he was becoming an addict to narcotics because of the frequent requirements of opiates. Pain at night was very common and very severe. Occasionally the patient would find that he could get some relief by lying on his stomach.

Physical examination revealed marked tenderness along the right rectus abdominis muscle. There seemed to be much spasm of the muscles in this area. The sedimentation rate was 97 mm in one hour. The value for serum amylase was 160 units. Roentgenograms of the stomach and duodenum disclosed a duodenal ulcer; gastric analysis showed values of 80 units for total acidity and 60 units for free hydrochloric acid. Material aspirated from the stomach amounted to 140 c.c. There was considerable blood in this material. The leukocyte count was 18,500 per cubic millimeter of blood. At operation a huge inflammatory mass was found to originate in the region of the first portion of the duodenum. This mass was 6 cm in diameter, it involved the lower end of the gallbladder in the region of the common bile duct and the area contiguous to the capsule of the kidney, as well as the mesocolon in that area.

We have seen other instances in which duodenal ulcers perforating into tissues contiguous to the kidney or involving the transverse mesocolon gave rise to a syndrome similar to the one just described. It should be remembered that the transverse mesocolon has a somatic nerve supply which extends to within an inch or two from the wall of the bowel.¹⁸ The segmental accumulation of nerve impulses from the mesocolon is in a level lower than that receiving the nerves which supply the lesser omental tissues. Pain impulses from these sources will be referred into a lower area than that originating in the lesser omentum.

SUMMARY OF SYNDROMES PRODUCED BY CHRONIC PERFORATING DUODENAL ULCER—Usually, the symptoms of the patient with peptic ulcer

have some features which are common to all cases. The majority of the patients experience a characteristic sequence of events. Since duodenal ulcer is, in so many instances, a recurring lesion, most of the patients have a long history. For years there may be exacerbations in the spring and fall, or five to six attacks a year, all with the typical visceral type of pain which generally is gnawing, rather diffuse in location over the epigastrium, and eased by the taking of food and milk. Then there is a progression of symptoms, the attacks become more frequent, the period in which the ulcer is quiescent is shorter and each attack is more severe and persistent. The simple methods of securing relief from pain by the taking of food and alkali are no longer efficacious. There may be, for the first time, episodes of vomiting. Nocturnal pain may develop between 1 and 2 a.m., becoming a frequent occurrence. There may be sudden seizures of vomiting resembling the so-called ulcer crisis. There may be a slight shift of the pain to the right of its original location and it may extend from the right upper abdominal quadrant into the back to the right of the eighth, ninth and tenth thoracic vertebrae.

But, when chronic perforation finally does occur into tissues surrounding the duodenum, the patient notices a shift of pain to secondary areas, the pain is more boring, sharp, severe and more localizable. Usually, the patient will not be able to continue working, he may be emotionally upset or depressed and usually will realize that some complication has radically changed the situation. He may need opiates for relief, this may be difficult for him to understand. He may be suspected, even by his physician, of being an addict to narcotics. Some of the patients have even undergone psychiatric treatment. Many of them will adopt bizarre postures for relief, such as the knee-chest position, and crawling on the floor on the hands and knees. We recently had one patient who dragged himself across the floor on his abdomen thus obtaining some relief. It seems that those lesions which perforate to the pancreas cause the most intractable and severest pain. Such patients are more likely to seek unusual postures for relief.

Referred pain brought about by invasion by a duodenal ulcer of the lesser omentum is likely to resemble the pain of disease of the gall bladder, since pain usually occurs across the lower and anterior part of the thorax, with predominance on the right side. The shift of pain to the back, between the shoulders, again is suggestive of cholelithiasis. We have seen patients who twice underwent surgical exploration of the gallbladder with negative results who proved to have chronic perforating lesions of the duodenum. If there is pain in the areas as mentioned above, and a previous history of ulcer, this possibility always should be kept in mind. If a lesion such as the suspected and surgical exploration reveals no obvious ulcer the

denum should be opened and clearly visualized, because some of the small perforating lesions may not be seen from the exterior of this organ. We believe it is likely that the shift of pain from the lesser omentum into the somatic areas occurs by means of the parietal referred mechanism, in the same manner that diaphragmatic pain is felt in the areas of the neck.

The pain of pancreatic involvement by a perforated duodenal ulcer is usually lower than the original visceral pain caused by uncomplicated ulcer and is often manifested around the umbilicus. In some instances, it may extend to a slight extent into either the right or left lower abdominal quadrants. Generally, however, the most typical finding is a severe pain in the back at the level of the first and second lumbar vertebrae. The afore-mentioned findings, along with the feature of the patient's putting his body in flexion or applying pressure over the upper part of the abdomen, and a history of duodenal ulcer, is almost certain to indicate pancreatic involvement by a perforated ulcer. It should be mentioned that pancreatic carcinoma and perforating gastric and jejunal ulcers into the pancreas may produce a similar picture.

In many instances, the sequences of symptomatic events from the simple pain of ulcer to the final chronic perforating stage is characteristic. However, sometimes recurrence of an ulcer may be an explosive occurrence without the mild type of antecedent history. The diagnosis may be problematic. Since so many chronic perforating lesions are situated on the posterior wall of the duodenum, results of roentgenologic study occasionally will be negative. It is under these circumstances that it is so important to recognize this syndrome clinically, if surgery is to be done, an exhaustive search should be made to find this chronic perforating lesion.

The diagnosis of this syndrome is made on the basis of the history, the sequence of symptomatic events, and especially on the mutations in the location and references of the pain which the patient experiences. As a rule, the physical observations are limited to some degree of deep tenderness over the duodenum. The roentgenologist most often finds a duodenal ulcer, but at times cannot tell that it is perforating. Results of roentgenologic examination may be negative, probably because of the situation of the ulcer on the posterior wall. If there is extension of the inflammation around the common bile duct, there may be slight jaundice, or occasionally, when the pancreas is involved, there will be an elevated value for serum amylase in the blood. These lesions often cause partial pyloric obstruction.

Duodenal Fistula.—Rarely a fistulous communication develops between the duodenum and some hollow viscus or the abdominal wall.

A fistula which results from a ruptured duodenal ulcer may occur

in several ways. The progressive inflammatory processes incident to the action of perforation by an ulcer may result in sealing of the duodenum to the surface of the gallbladder or against the biliary duct. When the actual perforation occurs, a fistula will be produced between the duodenum and the gallbladder or the bile duct. An illustrative case follows:

A man forty-nine years old presented himself for examination because of pain in the upper part of the abdomen. Three years before his consultation at the Clinic he had suffered a severe gastro-intestinal upset, during which he had experienced much vomiting and a marked intolerance of food. There had been some question as to a slight icteric tint to his skin at that time. Two months later he had had another attack of acute epigastric pain, after which blood had been found in the stools. For two months prior to his visit to the Clinic he had had epigastric pain daily, this pain arose three hours after the ingestion of meals and was relieved by vomiting. There was gradual progression of the symptoms, the pain, which previously had been periodic, became constant and severe. Physical examination showed nothing of importance. Estimation of gastric acidity showed values of 44 units for total acidity and 20 units for free hydrochloric acid (method of Topfer). There was definite evidence of gastric stasis, 765 c.c. of gastric contents being recovered. There was some evidence of toxemia, the value for urea was 59 mg. per 100 c.c. of blood, and the carbon dioxide combining power of the plasma was 72 volumes per cent. Roentgenologic examination of the stomach disclosed evidence of pyloric obstruction. After preliminary pre-operative treatment, he was operated on. He was found to have an acutely infected gallbladder and a duodenal ulcer which had perforated into the gallbladder.

There was some definite evidence in this case which would lead to suspicion of the presence of peptic ulcer. The hemorrhage and the association of epigastric pain appearing several hours after the ingestion of food would suggest that the primary lesion probably was in the duodenum. It is extremely unusual for a fistula between the gallbladder and the duodenum to occur in this way. The fistula usually develops after an acute condition in the gallbladder and subsequent involvement of the duodenum. Mason and one of us (Rivers) reviewed a series of 1,117 patients operated on for cholecystic disease. In nine of these a fistula between the gallbladder and the duodenum was found, however, in only one of these cases was the fistula the result of a primary lesion in the duodenum.

Occasionally, a fistula between the duodenum and the abdominal wall will be produced in an indirect manner. A subacute or acute perforation of a peptic lesion in the duodenum may result in the formation of abscess. This abscess becomes attached to the abdominal wall; ultimately it ruptures into the abdominal wall and a fistulous tract may break through, discharging pus and gastric contents into the epigastric region.

THE DIFFERENTIAL DIAGNOSIS OF DUODENAL ULCER

In the majority of instances, the diagnosis of duodenal ulcer can be

made rather easily. It is characterized by late, postprandial, burning epigastric pain that is relieved by the taking of milk and soda, and it is further featured by recurrent attacks and chronicity, present usually in an emotionally labile person who has a high gastric acidity. The diagnosis is verified by roentgenologic examination. In the preceding sections we have emphasized the importance of recognition of the syndrome of complicating penetrating lesions caused by involvement of extraduodenal tissues, a syndrome which produces a shift of pain to the right of the midline, to the right in the upper part of the abdomen, to the right in the back, to the lower anterior and posterior portions of the thorax, and in some instances to the right lower abdominal quadrant. Thus, keeping in mind the possibility that ulcers may produce such features as the foregoing, we must, in differential diagnosis, consider disease of the gallbladder, of the right part of the urinary system, of the right part of the colon, of the appendix, and skeletal pains in the right side arising from a diverse group of causes. We must also keep in mind that there may be coexistent disease in the stomach or esophagus.

Duodenal Ulcer Associated with Benign and Malignant Gastric Lesions.—In considering this possibility, the physician should have in mind the occasional coexistence of both gastric and duodenal ulcer, as well as the more rare lesion of cancer of the stomach which is complicating a duodenal ulcer. In 8 per cent of instances gastric and duodenal ulcers coexist. If the patient has a peptic ulcer and it has been shown to be duodenal in situation, the method of therapy can be decided on without consideration of any possibility that it may be malignant. If, however, the patient complains that pain has extended to the left upper abdominal quadrant, or if pain has projected itself into the left thoracic vertebral area, the physician should be suspicious that a second lesion is present in the stomach, and further search should be made to find it. Furthermore, if the roentgenogram reveals a duodenal ulcer and review of the symptoms brings out the fact that distress arises within an hour after ingestion of the meal and disappears spontaneously an hour or so before the next meal, the suspicion may be well grounded that a second ulcer exists in the stomach.

Wilbur and one of us (Rivers) studied the question of coexisting cancer of the stomach and duodenal ulcer, and found that such a condition is rare indeed. It is important, however, to remember that the two conditions can coexist, and to realize that discovery of a duodenal ulcer does not exclude the possible presence of gastric cancer. Therefore, if the symptoms are not typical of duodenal ulcer, if there is a short history of a vague type of epigastric distress which arises shortly after ingestion of a meal and which remains unrelieved by food or all ali, and if the signs of anemia, loss of weight, low gastric acidity and retention are present, the suspicion of an associated malignant

process in the stomach should be entertained. Discovery of an epigastric mass may corroborate this suspicion, and if roentgenologic examination fails to discover the lesion, it might be well to inspect the tissues directly by means of the gastroscope.

When the subject of gastric cancer associated with duodenal ulcer is considered, the fact should be mentioned that many malignant lesions of the stomach produce symptoms closely simulating those caused by peptic ulcer. The physician, therefore, never should make a presumptive diagnosis of duodenal ulcer without a careful roentgenologic examination. Nor should the evidence of normal or elevated values for hydrochloric acid in the gastric contents as obtained by a test meal give false assurance to the physician. Dry and one of us (Rivers) found that in most instances, when malignant gastric ulcers produce symptoms suggestive of peptic ulcer, normal or even accelerated rates for the secretion of gastric acids were present.

Generally, the diagnosis of frank carcinoma of the stomach can be determined without difficulty by roentgenologic investigation. This investigation occasionally will not suffice for distinction between malignant and benign gastric ulcer. The gastroscope may help, but in certain instances this instrument likewise will not adequately distinguish the lesions. If a patient who is receiving adequate medical treatment for duodenal ulcer does not respond satisfactorily, and if occult blood continues to be present in the stool, grave suspicion of the possible presence of a malignant process in the stomach should be entertained.

Duodenal Ulcer and Cholecystic Disease.—The two most common causes of indigestion among patients older than forty years in a series of more than 4,000 patients studied by Ferraira and one of us (Rivers) were found to be peptic ulcer and cholecystic disease. Of men older than forty years who had indigestion, 23 per cent were found to have peptic ulcer and cholecystic disease. Of the women with indigestion in that age group, 24.5 per cent had cholecystic disease and 9.5 per cent had peptic ulcer. These two diseases exceeded even functional diseases as the cause of indigestion among dyspeptic patients more than forty years old as seen at the Clinic.

Failure to make a correct differential diagnosis between these diseases or to recognize the fact that peptic ulcer may be associated with cholecystic disease may result in the advising of treatment which is detrimental rather than helpful to the patient.

It is unusual for any difficulty to arise in the distinction of complicated duodenal ulcer from disease of the gallbladder. There are system and order in the natural history of duodenal ulcer, there are periodic attacks, often in the spring and fall, which persist a week or two and are followed in due time by complete abeyance of all symptoms. Pain arises at a definite time two or three hours after ingestion of a meal, to be relieved promptly by the taking of food or an alkali.

The syndrome of cholecystitis, on the other hand, lacks regularity and order. Distress usually occurs after the ingestion of certain foods, such as fried foods, cabbage, onions or apples. This distress, which is characterized by a feeling of fullness and distention, arises after the meal is eaten, frequently it is associated with nausea and vomiting. The distress is irregular in duration. Generally, tenderness is present over the region of the gallbladder. Very rarely, however, cholecytic disease produces symptoms which resemble those caused by duodenal ulcer. Distress which as a rule is more of the flatulent type may be manifest several hours after the meal, and may be relieved by an alkali. Usually, this occurs in a stout woman in whom disease of the gallbladder might be suspected. The syndrome of cholecytic disease lacks some of the features of the syndrome of duodenal ulcer, as a rule it mimics the syndrome of ulcer only in part. Under such circumstances, if several roentgenologic examinations have not demonstrated a peptic ulcer, cholecystograms should be made, these generally will disclose a malfunctioning organ or gallstones or both.

Subacute perforation of a duodenal ulcer may produce a picture with some features simulating those of acute inflammation. Generally, the pain caused by such a complication is felt severely in the upper and right portion of the abdomen, and a mass may develop which could be mistaken for a distended gallbladder. The extension of pain into the area of the right lower scapula is not unusual when a duodenal ulcer exhibits the complication of perforation, and this further complicates the diagnosis. On the other hand, subacute complications occur almost exclusively in the presence of chronic ulcer, and therefore the history usually can be depended on to disclose the characteristic attributes of duodenal ulcer for some time before perforation occurred. After the acuteness of the condition has subsided, the roentgenologic examination will disclose the deformity of the duodenum, which then permits arrival at a correct diagnosis.

There is very little in the syndrome of peptic ulcer which could be confused with the manifestations of gallstone colic. This type of colic begins and stops suddenly, often without good dietetic reason. The pain is severe, extends to the right costal arch and through to the back or the scapular region. Generally, there is a sense of severe upper abdominal pressure frequently accompanied by nausea and vomiting. The attack may terminate spontaneously after vomiting or vigorous belching, or it may require the use of opiates. The return to comfort is rapid, and unless a complicating inflammatory condition is associated, there is very little residual manifestation to show that anything unusual has occurred in the upper right abdominal quadrant.

The greatest difficulty in distinction between peptic ulcer and cholecytic disease occurs in the case of chronic perforating duodenal ulcer in which the ulcer invades tissues contiguous to the gallbladder or

even that organ itself. The situation of the pain in these lesions is in the area of the gallbladder. Furthermore, the pain is referred into the right part of the thorax or into the back, to the right of the lower thoracic vertebrae, just as it may be referred in acute cholecystitis.

To add to the difficulty, many of the patients complain of much upper abdominal distention. Often, at the height of the pain, there may be nausea and vomiting. The history, however, usually includes a prolonged record which suggests peptic ulcer, and sufficient characteristics of ulcer remain, such as intensification of pain several hours after meals and ease obtained by alkali, to suggest that diagnosis. The vomitus may contain blood, frequently there is evidence of occult blood in the stool, both of which signs suggest the presence of peptic ulcer. Evidence of biliary obstruction is shown by the presence of jaundice and light-colored stools, an increased content of bilirubin in the blood would certainly tend to involve the gallbladder or the bile ducts. Roentgenologic examination affords the only certain preoperative means of distinction between the two conditions. If the syndrome has definite characteristics of associated lesions, a cholecystogram also should be made.

Neurasthenic Dyspepsia.—Functional disturbances are by far the most common causes of indigestion. Twenty-seven per cent of patients who come to the Clinic because of indigestion are believed to have a nervous type of dyspepsia. Inasmuch as peptic ulcer is next in frequency of occurrence as the cause of indigestion, it can be seen how frequently the physician might be called on to distinguish between the two conditions. Actually, two of every five patients, young or old, men or women, who present themselves because of indigestion have either peptic ulcer or functional indigestion.

The appearance of the patient who has duodenal ulcer might easily give the impression that the symptoms to be discussed may not have an organic basis. Most of the patients are of the nervous, tense, restless type. Often they smoke three or four cigarets while they are giving a recitation of their symptoms. However, it seldom is longer than a few minutes before the story so suggestive of peptic ulcer unfolds itself, if the patient has such a lesion.

On the other hand, the nervous dyspeptic patient rarely presents a group of symptoms which are well ordered and follow a definite pattern. Generally, the symptoms occur daily, in fact, many patients have constant symptoms. "There is always something wrong," is the complaint. It may be headache or nausea and vomiting or constipation or pains in the joints or gas on the stomach. The dyspepsia may exhibit qualitative food relationships. The patient cannot eat this food or that, and yet the next day the same article of food may be eaten with impunity. Even milk causes distress, indeed, even water may

make the patient belch, and usually this is demonstrated forcefully, dramatically, loudly and frequently "Sour stomach" is complained of frequently, and often there is regurgitation of material which is said to be so "acid it cuts the teeth," when in reality analysis of a test meal may show complete absence of free hydrochloric acid.

The important feature of the history is that it lacks consistency, and so it seldom should be confused with the story of duodenal ulcer. A diagnosis, however, must not be made on the basis of the history alone, because many organic diseases, including peptic ulcer, are masked under the personality of the neurotic patient. Hence, it is always essential that organic disease be ruled out by a complete examination, including laboratory tests. Symptoms which distress the patient while he still is at the table are most unlikely to be those of ulcer. A simple question as to the presence or absence of such prandial symptoms is a valuable diagnostic aid.

Duodenitis.—It may be impossible to distinguish accurately between duodenitis and duodenal ulcer. Several years ago we reviewed carefully the records of seventy-five patients who had been found at operation to have nonulcerative duodenitis. We were attempting to formulate a syndrome sufficiently definite for it to be possible to demarcate it from duodenal ulcer. Patients who have nonulcerative duodenitis are of the same type as those who are likely to have duodenal ulcer, that is, the age group is the same, and the incidence according to sex is identical. Interestingly, the afore-mentioned patients with duodenitis had experienced symptoms for an average of a little less than eight years.

Duodenitis, although not complicated by ulceration, frequently is found to involve intensively the muscularis and serosa as well as the periduodenal tissues. The pain is likely to be less definitely localized to a small area in the epigastrium than is true in cases of uncomplicated peptic ulcer, and often the area of which maximal complaint is made is not designated as epigastric, but rather, as being diffusely distributed through the entire upper right abdominal quadrant.

Often the complaint is not of pain, but of nausea and a distressing sensation of fullness in the upper right part of the abdomen. Although this sensation might arise shortly after meals, it usually reaches maximal intensity several hours after the ingestion of food. The patients in our series resorted to the use of alkalis more frequently than to food to obtain relief from symptoms.

Jaundice very rarely occurs in the presence of duodenitis, although at operation pathologic change in the gallbladder was not demonstrable in the series we have mentioned. In such instances, the jaundice probably was the result of the extension of the inflammatory process to the ampulla or of an associated infectious process in and along the biliary ducts.

Kirklin reviewed the roentgenologic data in a series of cases of duodenitis. He noted certain differences, roentgenologically, between duodenitis and frank duodenal ulcer. The most significant of his observations appear to be the following: "As a rule the bulb is quite irritable, greatly deformed and diminished in size, often it is represented by a mere skeleton of barium content. Margins of the bulbar shadow tend to be hazy and indistinct." Apparently, the pylorus ventriculi is highly irritable and is characterized by rapid emptying, so that it is difficult for the bulb to be filled for any length of time, and the spastic deformity is not only more pronounced than that produced by a true ulcer, but it is also more unstable.

Pseudo-ulcer.—One of the functional conditions most puzzling to distinguish from duodenal ulcer is the "ulcer syndrome without ulcer" or, as it is called by Alvarez, the "pseudo-ulcer." The condition has all the features of duodenal ulcer, with periodicity, punctuality, and the food-case sequence, except that the roentgenograms disclose nothing abnormal. In many instances the patients have undergone surgical exploration, and the surgeon, not being satisfied with the absence of a visible or palpable lesion, may have cut open the stomach and duodenum, only to find them perfectly normal. It is most likely that the symptoms are the results of pylorospasm. It has been shown that even in the achlorhydric stomach soda sometimes will relieve the symptom of heartburn which is due to spasm in the lower end of the esophagus. There seems little doubt that the ulcer-like syndrome which occasionally is described as an actual ulcer syndrome occurs in nervous, highstrung, intense persons, and that it is particularly likely to be established during periods of fatigue and tension. Because peptic ulcer also is seen frequently in cases similar to those described, because re-establishment of ulcer frequently takes place after periods of stress, fatigue and tension, and because fluctuating psychophysiologic factors seem capable of preventing cessation of the ulcer syndrome, it is suggested that factors which have their inception in derangement of the nervous system must be of some significance in the cause and course of an ulcer-like type of syndrome, whether or not ulcer is present. After this syndrome has been established for a prolonged period, it is conceivable that the pylorus, which certainly participates in the formation of this syndrome, actually may become hypertrophied or stenotic. The following case is an interesting illustration of this fact.

A woman, twenty-seven years old, with a high-tension and driving personality, had had heartburn since early childhood. For three years prior to her registration at the Clinic, she had had an ulcer type of distress characterized by moderately severe, gnawing, nonextending pain which was localized in a small area to the right of the epigastrium, and which occurred about forty-five minutes after eating.

On physical examination, Wilms' tumor is to be differentiated from other abdominal enlargements, viz, hepatomegaly, splenomegaly, hydronephrosis, polycystic kidney, omental cyst, tuberculous peritonitis, neuroblastoma, Hodgkin's disease, lymphosarcoma, leukemia and teratoma

Roentgenographic examination will usually establish a presumptive diagnosis

Biopsy is contraindicated as a diagnostic procedure for Wilms' tumor since this tumor is highly malignant and metastasis may follow such a measure

TREATMENT—Management is by surgical removal, as early as possible, depending on the size of the tumor. Since this growth is very radiosensitive, some surgeons prefer administering preoperative x-ray therapy in order to reduce the mass and thus to simplify the operation. Most surgeons, though not all, consider postoperative irradiation important.

It is believed by Ladd⁸ and others that any patient who has survived two years following the removal of the tumor has a probable cure

Testicular Tumor—A testicular tumor occurs as an enlargement of one testis, usually painless in the beginning. The children who are affected are of the preschool age. If the tumor is a teratoma, there may be endocrine manifestations.

A testicular tumor is to be differentiated from orchitis, hematoma, hernia and hydrocele.

TREATMENT—This consists of orchidectomy preceded by irradiation.

Prostatic Tumor—An increasing number of sarcomas of the prostatic region and vesical neck have been reported in small infants.

The diagnostic criteria are symptoms of urinary obstruction, producing dysuria, and at times hydronephrosis with secondary pyonephrosis. The condition is to be differentiated from congenital malformations of the urethra and bladder which also produce obstructive urinary symptoms.

TREATMENT—Management has been unsatisfactory in the several cases I have observed because of the diffuse, infiltrating nature of the tumor which precludes adequate surgical removal. Treatment by irradiation has been undertaken too late to evaluate its usefulness.

Ovarian Tumor—The occurrence of an ovarian tumor in a child is very unusual. Most of them occur during early puberty but I have observed such a tumor in a child as young as two years. Ovarian cyst, carcinoma of the ovary, teratoma, and granulosa cell tumor are among the neoplasms more frequently described.

The presence of a pelvic mass which may or may not produce pressure symptoms in the intestinal tract is usually clinically diagnostic.

The pain could be relieved for a short time by the taking of food or soda. More prolonged relief was obtained from the eating of larger meals and coarse foods. The symptoms were incapacitating, but not because of their persistence. Emotional or psychic strain aggravated the distress. Nausea frequently occurred immediately after the taking of food, but could be controlled by the use of belladonna. There was no vomiting, but the patient occasionally felt that food did not pass out of her stomach promptly. There was no history of gross bleeding, and occult blood was not found in the stools.

Tenderness or localized muscle spasm was not elicited on examination. Values for gastric acids were high, that for total acidity being 74 units and that for free hydrochloric acid being 62 units (method of Topfer). Repeated roentgenograms disclosed a rapidly emptying stomach without a demonstrable lesion. Because of such observations and because of failure of the patient's condition to respond to a strict medical regimen, it was suspected that the condition was due to pylorospasm.

At operation hypertrophy and partial stenosis of the pylorus, with thickening of the muscle of the antrum, were found. The appendix had been removed many years previously. The anterior segment of the pyloric muscle was excised, and closure was completed as in gastroduodenostomy. There was no improvement for eight months, then the distress progressively lessened.

The history in this case illustrates most of the features we have come to consider as characteristic of the ulcer syndrome without ulcer, but with pylorospasm. The patient was of the high-strung temperament so often noted in cases of ulcer, and neurogenic factors were prominent in aggravating the distress. The whole picture, so far as symptoms were concerned, was that of ulcer of a severe type. Yet, as opposed to such a picture, the relief obtained by the taking of food and alkali was too transient, improvement was not attained by careful treatment in the hospital, the element of periodicity was not present, there was no localized tenderness, blood was never detected in the stools, and the results of roentgenoscopic examination were repeatedly negative. It is of interest to notice that this patient's father subsequently manifested almost identical symptoms, especially so far as the influence of neurogenic factors in the aggravation of symptoms is concerned. In his case, however, duodenal ulcer was demonstrable in the roentgenogram.

There are several factors which can be utilized in the distinction of these conditions from those in patients who usually have peptic ulcer. Distinction may be extremely difficult if the duodenal ulcer is uncomplicated, even though several factors which are suggestive are obtainable by the careful taking of clinical history. The symptoms in the ulcer syndrome without ulcer usually are milder, and there are seldom any recurrences of difficulty at night.

The general average of gastric acidity is about the same in the two conditions. Roentgenologic examination may show some evidence of pyloric stenosis. However, in most instances, there is no evidence of a duodenal niche or the characteristic crater of an ulcer.

Benign Lesions of the Pancreas.—Comfort, Gambill and Baggenstoss recently reviewed in great detail the symptoms of chronic relapsing pancreatitis. The symptoms of this condition or of its occasional associated complication of acute pancreatitis and pancreatic lithiasis occasionally may cause some difficulty in the diagnosis of duodenal ulcer. In such cases it occasionally is found that pain is present which might be confused with the pain of peptic ulcer. The general characteristics of the pain are not those of the pain of ulcer. The situation, however, might present some confusion so far as perforating duodenal ulcer is concerned. Comfort and associates found that the patients in question complained of distress in the right upper abdominal quadrant, and that occasionally this pain was referred through to the region of the lower thoracic vertebrae and, more rarely, to the lower right abdominal quadrant. In some instances, the pain was cramping, in others, it was more of a gnawing steady type, such as characterizes peptic ulcer which is perforating to the area contiguous to the gallbladder or to the pancreas. Furthermore, a number of the patients in the afore-mentioned study complained that the pain occurred in attacks lasting two to thirteen days.

The pain of a penetrating type of peptic ulcer may occur in attacks which last a similar length of time. In pancreatitis, however, there is seldom anything similar to the syndrome of peptic ulcer, that is, relief is not obtained by the use of food or alkali. The patients seldom have pain which arises two or three hours after the eating of a meal. Food is more likely to start than to stop the pain. Also, later in the course of the disease, relapsing pancreatitis is likely to manifest itself by disturbances of function of the acinar and islet cells and by certain sequelae. At first, disturbances of function may be of short duration and mild during the acute phase, before widespread anatomic destruction has occurred. When such destruction has developed, glycosuria and hyperglycemia, steatorrhea and creatorrhea may appear and persist. Investigation of the area may disclose pancreatic stones or calcification, the pancreas may become enlarged and palpable. Some of the sequelae of this disease are obstruction of the common bile duct, with jaundice, hepatitis and distention of the gallbladder.

It must be remembered that occasionally this disease also results in obstruction of the duodenum because of enlargement of the pancreas.

Appendicitis.—Acute appendicitis when associated with peritonitis, particularly if the appendix is ruptured, may require careful consideration in distinction between that condition and subacute or acute rupture of a duodenal ulcer. The causal relationship of recurring inflammatory appendicitis to dyspepsia has been the subject of much controversy. Yet, this type of appendicitis was considered of im-

portance in only 2.2 per cent of 4,223 cases included in a study of the causes of indigestion. In most of the cases in which recurrent appendicitis was considered to be the cause of indigestion, the condition occurred in young persons between the ages of fifteen and twenty-four years. In all probability, this type of appendicitis should be classified as subacute, rather than chronic, appendicitis. In only 2 per cent of women older than thirty-nine years included in this series was appendicitis considered to be the cause of chronic recurring indigestion. In only seven of 1,377 men more than forty years old did chronic dyspepsia appear to have been caused by chronic appendicitis. When the records in this study were more carefully studied, it was possible to find only two in which there seemed unquestioned evidence that the removal of a chronically inflamed appendix relieved the symptoms of indigestion for which the operation was undertaken.

We were of the opinion, after reviewing all these records, that appendectomy carried out for the relief of chronic recurring indigestion in patients older than twenty-five years usually produced a therapeutic result equally disappointing to the patient and to his surgeon. It has been postulated that disease in the region of the appendix may cause epigastric discomfort through a so-called ileogastric reflex. Often, the pain of a duodenal ulcer is somewhat relieved by elimination of constipation. It is possible that distention of the colon could cause increased pylorospasm.

Diseases of the Colon.—Generally, there is very little difficulty in distinction between duodenal ulcer and diseases which affect the colon. Hurst described two instances in which a patient who had malignant disease complained of symptoms suggestive of peptic ulcer. The pain in both instances was located in the right side below the level of the umbilicus. The therapeutic response was not characteristic of peptic ulcer; no relief was achieved by a medical regimen. Because there was blood in the stool and no duodenal deformity, a roentgenogram of the colon was made which disclosed the presence of a filling defect suggestive of carcinoma.

Diverticulitis of the colon seldom occurs in the area of the hepatic flexure, but when it does, the local inflammatory reactions may suggest the possibility of a penetrating or perforating type of duodenal ulcer. Lack of a history characteristic of ulcer and negative results of roentgenograms of the duodenum should leave little doubt as to the diagnosis.

Diseases of the Right Kidney.—There is nothing in the history of uncomplicated duodenal ulcer which should make it necessary to consider renal disease in the differential considerations. This is not true, however, of perforating duodenal ulcer which encroaches on the transverse mesocolon or the renal capsule. In such instances the ex-

tension of pain easily may be confused with that caused by renal or ureteral stone or even a malignant process of the kidney, or hydro-nephrosis. Because of the situation of the distress, then, it may be necessary to investigate the kidney by roentgenologic examination. Occasionally, intravenous urography or retrograde pyelography may be necessary adequately to rule out renal disease in such instances.

Carcinoma of the Duodenum.—Primary carcinoma of the duodenum is an extremely rare disease. Eusterman, Berkman and Swan reported fifteen such cases, and pointed out that the symptoms which such carcinoma caused were primarily those associated with obstruction of the bile ducts or the lumen of the duodenum. Dixon, Lichtman, Weber and McDonald reported forty-five cases of primary malignant lesions of the duodenum. They ventured the opinion that diagnosis of this condition usually is possible if the clinical history is carefully evaluated, with the roentgenologic examination extended to include the entire duodenum. The average age of the patients included in this series was 55.4 years. Fourteen of the lesions were found to occupy the first, fifteen the second, and twenty the third, portion of the duodenum. The most significant among the clinical manifestations included in this series were obstruction, bleeding, chronic perforation chiefly to the pancreas, and jaundice. An important diagnostic feature is that jaundice is preceded by signs of obstruction. Such a symptom should lead to the suspicion that a malignant lesion of the duodenum may be present.

Pain is the most common of all the complaints voiced by the patients. It is very similar in situation to that experienced by patients who have duodenal ulcer. It is epigastric or situated in the upper right abdominal quadrant. When perforation of a duodenal ulcer to the pancreas occurs, it is likely to refer pain into the back, just as is ulcer which is perforating to the pancreas. Furthermore, this pain which recurs at night is not an uncommon symptom in the presence of a duodenal malignant process. The distress frequently begins one hour to four hours after the ingestion of food, and may be relieved by the taking of alkali or by vomiting. The patients do not, as a rule, resort to the use of food to make themselves more comfortable.

From the foregoing description of the pain pattern exhibited by patients who have a malignant lesion of the duodenum, it is obvious that the differential diagnosis between such a lesion and duodenal ulcer might be impossible. This demonstrates again the necessity of utilization of all available data and bringing them to useful evaluation in particular instances. As a rule, patients who have a malignant lesion of the duodenum are older than those who have a duodenal ulcer. The duration of symptoms of the malignant process is shorter and symptoms are more severe. The characteristic intermittency of

the syndrome of duodenal ulcer is usually absent in the presence of a malignant duodenal lesion. Relief of symptoms by the approved medical methods of treatment of ulcer is not obtained. Estimation of gastric acidity usually reveals normal or low values. Generally, there is evidence in the stool of occult blood.

The picture presented by the syndrome of a malignant lesion of the duodenum generally is that of an older patient, with the situation of pain suggesting perforating duodenal ulcer or cholecystic disease with a relentlessly progressive course, which as time goes on exhibits singly or in combination signs of obstruction, hemorrhage, jaundice, and chronic perforation to the pancreas, and has the roentgenologic signs of a duodenal lesion. Physical examination may disclose a mass in the right umbilical region. Rarely, the gallbladder may be palpable.

Diverticulum of the Duodenum.—It may be difficult to distinguish between (1) a true diverticulum of the duodenum, which is a herniation of the duodenal mucosa through a weak point in the muscular layer, the fundus of the sac, as a rule, being devoid of musculature, and (2) pouching of the duodenum. A diverticulum of the duodenum usually produces no symptoms. If large, it may produce some nausea, vomiting or a sense of fullness without the characteristic periodic attacks of duodenal ulcer.

Meckel's Diverticulum.—Sometimes, ectopic gastric glands are found in the mucosa of a Meckel's diverticulum. In a series of 152 cases of Meckel's diverticulum studied by Carlson, he found some heterotopic tissue to be present in 27.6 per cent of cases. Ordinarily, these heterotopic regions are small, and their secretion is rapidly neutralized and dispersed. There are instances, however, in which a peptic ulcer occurs either in the area within that part of the diverticulum which does not have gastric glands. More frequently the ulcer is found in an area of the ileum on which the product of these glands flows.

The symptoms of ulcer of a Meckel's diverticulum are extremely variable, and in all probability they represent largely those related to complications such as penetration or hemorrhage. Dixon, Dueterman and Weber reported, in a study of Meckel's diverticulum, that the patients may have attacks of cramplike pain in the region of the umbilicus. They also reported that in two cases of ulcer of a Meckel's diverticulum the patients noted that the pain ceased two or three hours after the ingestion of food. Several years ago we reported four cases in which ulcer occurred about a Meckel's diverticulum, and we were unable to detect any of the usual characteristics of the pattern of pain usually produced by uncomplicated peptic ulcer.

Superficial or Radicular Pain.—Pain arising within the confines of the abdominal wall, and not related to any of the underlying organs,

is one of the commonest findings in the practice of medicine. Yet, in so many instances, the physician searches first for the obscure basis and last for the superficial basis. Such types of superficial pain have had many names, such as "muscle-wall pain," "skeletal pain," "radicular syndrome," "myalgia," "muscle strain," "neuritis" and many others. Most of these pains do not have the clear-cut features of root pain, nor are there sensory changes. They are a bizarre group, but there are a few features which are common, usually, mechanical factors such as stooping, twisting, lifting and working cause or aggravate the condition.

This type of pain as a rule resembles the pain of duodenal ulcer only in situation. The clinical sequence is *entirely different*. Whereas the pain of ulcer is usually related to meals and is intermittent in character, many superficial pains will be *mildly constant* throughout the day and night. Often, this pain will have arisen after an injury, or a day's work in which the patient has used muscles not ordinarily exercised. In many women the onset will take place after a day of housecleaning. Generally, constant jarring, such as riding in a truck, tractor, train or wagon, will aggravate the pain. It should be mentioned that constant jarring in many instances will also intensify the pain of a duodenal ulcer. In the presence of many of these types of vague pain there will be cutaneous hyperesthesia and tenderness of deep muscles which is not easy to distinguish from the tenderness to palpation of a duodenal ulcer, but with flexion of the abdominal muscles it usually can be shown that the pain is situated in the abdominal wall. Care must be exercised in the diagnosis of these pains, however, since the pain of perforating duodenal lesions in various areas, as mentioned earlier in this paper, may produce a very similar picture. According to the basic ideas of Lewis, purely visceral pain may be referred to the body wall and give superficial tenderness and hyperesthesia. Some writers, such as Morley, deny this mechanism of the production of pain. Roentgenograms of the spinal column occasionally will disclose some degree of hypertrophic arthritis which may be responsible for the pain. As a rule, if the phenomenon of superficial pain is remembered and its features sought for, the careful taking of a history will illuminate the subtleties of the problem.

Epigastric Hernia.—Occasionally, a weak spot in the abdominal wall will be found to explain the situation of pain which may have been attributed to gastric or duodenal ulcer. An epigastric hernia situated above the umbilicus in the linea alba is not an uncommon cause of such pain. Herniation may occur in a tiny portion of weakened abdominal wall, or the hernia may be large, resulting in a mass which includes some intra-abdominal structures. Frequently, there are such regions around the umbilicus. They may be found to be related in

some way to the incisions of previously performed surgical operations, in which case they are called "postoperative ventral hernias"

These areas may be very tender. Occasionally they cause spontaneous pain because of temporary fixation of some abdominal viscus in the hernia. What has been said of the differential diagnosis of dyspepsia in the presence of skeletal pains applies here. The examining finger generally will disclose these defects in the abdominal wall.

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Inasmuch as some ovarian tumors possess endocrine activity, somatic alterations, early menstruation and menorrhagia may occur

The nonendocrine varieties are differentiated from pelvic lymphomas and neuroblastomas by the size which they attain without producing blood changes or metastasis

TREATMENT—Surgical removal should be carried out wherever possible. If the tumor is malignant, postoperative irradiation should be instituted

Myosarcoma of Vagina (*Sarcoma Botrioides*)—This tumor of the vaginal wall is symptomless until vaginal discharge occurs or until part of the tumor protrudes from the vaginal outlet

This neoplasm is to be suspected in a child who has a persistent mucoid or bloody vaginal discharge, at any age. If necessary, an examination under anesthesia should be performed to establish the diagnosis. It is to be differentiated from infections which produce similar discharges

TREATMENT—Surgical removal followed by irradiation is the preferred management. The tumor is highly malignant

TUMORS OF SOFT SOMATIC STRUCTURES

Tumors of the supporting structures, including fat, muscle, connective tissue, nerve and synovial sheath, are not uncommon. They may be either benign or malignant and have been observed in some cases to persist for a number of years before undergoing malignant transformation. These tumors appear at any age, not uncommonly at or shortly after birth. They have the appearance of an innocuous swelling and cause no subjective symptoms. There may be no tissue enlargement until a malignant clinical course is reached

Any swelling which is nontraumatic in origin or a traumatic swelling which does not regress in the usual time should be considered cancer until proved otherwise

While most are solid tumors and frequently feel firm, they may be deceptive in many cases, suggesting soft tumors or even cysts, depending upon their tissue components and their position in relation to the body surface. The consistency will be more readily determined if they are situated near the skin than if the insulating layers of fat and fascia interpose between the tumor and the examiner's hand

TREATMENT is by complete excision when surgically feasible. Amputation of an extremity may have to be considered. Irradiation may be indicated in some instances

Hemangioma.—This is the most common tumor observed in Memorial Hospital among white children. The great majority are observed usually during the first year of life. According to Watson and McCarthy,⁴ 80 per cent occur during the first year, with 70 per cent during the first month. More girls are affected than boys and the most

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SYMPOSIUM ON SPECIFIC METHODS OF TREATMENT

THERAPEUTIC CONSIDERATIONS IN SUBACUTE AND CHRONIC HEPATITIS

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THE patient with one of the many forms of chronic hepatitis may today look forward to a far more favorable life expectancy, comfort and earning capacity than he could a decade ago. This improvement in prognosis may be ascribed in part to recent advances in the knowledge of hepatic physiology which have resulted in new therapeutic approaches and pharmacologic agents, in part to a better understanding by the average physician of the natural course of this group of hepatic diseases, and in part to the increasing opportunities available for the study of the pathologic processes involved in the development, through all its various phases, of so-called cirrhosis. Neither time nor progress, however, has altered the fundamental principles of treatment, these are the provision of an adequate, well balanced diet and, by limiting physical exertion, the restriction of the daily metabolic demands upon a damaged liver.

So-called cirrhosis is, of course, not a single disease entity but represents a huge number of inflammatory and degenerative processes in the liver, manifested histologically by varying degrees and combinations of cellular necrosis, fatty infiltration, inflammatory reaction and

From the Department of Medicine, Harvard Medical School and the Medical Service of the Massachusetts General Hospital. We are indebted to Dr. Tracy B. Mallory for the histologic descriptions and interpretations of biopsy specimens and to Mrs. Clara Edwards for technical assistance.

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fibrosis The combination of all these abnormalities is most common in that variety of chronic degenerative hepatitis associated with malnutrition and the intake of alcohol. The role of alcohol in such liver disease remains far from clear although it seems that its major effect may be that of chronic protein starvation produced by its use as a substitute for food. As emphasized by Bloomfield,² the histologically stationary, end-stage picture of nodular regeneration and fibrosis is usually the result of prolonged smoldering of an active, inflammatory, degenerative process. During the course of the development of this final histologic phase, there often occur acute exacerbations interspersed with symptomatic and histologic remissions.

VALUE OF LIVER BIOPSY

What may be accomplished therapeutically at a given time will depend upon the histologic state of the liver at that time and upon the accumulated amount of architectural damage as compared with the degree of and capacity for new parenchymal cell regeneration. A liver biopsy therefore, obtained by needle or peritoneoscopy soon after the patient comes under observation, is very desirable for indicating the optimum duration of strenuous therapy, the immediate clinical response to be expected from it and the long-term prognosis.³ Complete clinical and laboratory data often give a false or inadequate idea of the underlying histopathology. Marked functional improvement obviously cannot be expected in histologically stationary liver disease, whereas in an acute degenerative fatty liver associated with malnutrition, with or without the addition of alcohol, a relatively optimistic outlook is reasonable. In the latter instance, the reparative processes of parenchymal regeneration are usually very active. The discovery of an acute inflammatory reaction indicates prolonged careful treatment with marked restriction of the patient's physical activity.

DIET

The foundation of successful treatment of any chronic hepatitis lies in the administration of a diet adequate in calories, in protein and in carbohydrate.³ We suggest a daily intake of 40 to 50 calories with 1.5 to 2 gm. of protein per kilogram of body weight. The old question of the proper ratio of dietary fat and protein is no nearer settlement than it was ten years ago. It has, however, become apparent that the rigid restriction of fat, such as the former "fat-free" diets demanded, is not only unnecessary but undesirable, because the resultant untalibility lowers the total caloric intake. In animals the experimental production of dietary and toxic hepatic injury has shown beyond doubt that a high intake of fat will markedly augment damage incurred during a low protein diet. If, however, the protein intake is

common site is about the head and neck. Although most hemangiomas are benign, some are locally malignant and others may metastasize.

Hemangiomas occur in the skin, subcutaneous areas, viscera, bones, and cranial cavity. An unusual case observed in our series showed hematopoiesis in the vascular walls.

The diagnosis presents no difficulty, as a rule, but it should be recalled that there are several varieties of this tumor which are of definitely serious import to the patient. These are (a) visceral, osseous and intracranial types, (b) locally malignant types, (c) metastatic hemangioma, (d) benign lesions which may cause impaired function of the body area affected (for example, those occurring about a joint), and (e) those which produce disfiguring scars.

Ecchymoses in the newborn may resemble hemangiomas, particularly those which occur as the result of constriction of the head by a tight cervix. These resemble the *nevus vinosus* but usually disappear promptly, whereas the hemangioma generally does not appear until some days after birth. Stellate (spider) hemangiomas at times resemble metastatic bacterial petechiae but may be distinguished by the fact that the hemangioma fades on pressure.

Subcutaneous hemangiomas may resemble cysts, lipomas or other soft part tumors. Many hemangiomas occur in the deeper tissues—brain, eye, larynx, mediastinum, liver, kidney and bones.

Wherever roentgenograms can be obtained, as in the skull and bones, rather constant features, namely, linear striations, are seen and are diagnostic. Opaque areas (intracranially or elsewhere) are associated with calcified hemangiomas.

The presence of this tumor should be suspected in visceral bleeding, especially if unaccompanied by evidences of infection. In general, cutaneous hemangiomas are present if visceral lesions exist but this is by no means constant. Johnston⁵ of Binghamton, New York, observed two cases of mediastinal hemangiomas in early infancy unaccompanied by cutaneous lesions.

TREATMENT—From the therapeutic standpoint, it should be recognized that 80 per cent of hemangiomas occur during the early years of life and most of them appear before a child is one year of age.

Treatment may be deferred on the supposition that, as not infrequently happens, the vessels of the tumor will thrombose spontaneously and regression will occur. The patient requires close and frequent observation early in life to determine whether the tumor is growing at a rate which will necessitate extensive, prolonged therapy later. Therefore, hemangiomas which are discovered within the first eight weeks of life should be examined and measured at least several times a week.

The simple varieties of capillary hemangioma respond to the application of carbon dioxide snow for five to fifteen seconds. Some cavern-

maintained at a high level, there is as yet no real evidence that a moderately high fat intake will harm the liver or enhance toxic injury.

Intravenous and Oral Supplements—In order to insure an adequate caloric intake in the acute phase of chronic liver disease, where oral feeding is difficult, certain intravenous supplements are useful. Since only *oral* feedings can provide a complete variety of dietary essentials, tube feedings offer the best solution to the problem of a persistently low spontaneous food intake. At the present time, transfusions of pooled plasma are not only inefficient in providing a satisfactory nitrogen intake but present also the serious hazard of subsequent serum hepatitis, while blood transfusions are indicated if anemia is present. Protein hydrolysates, when given intravenously, are relatively ineffective for furnishing a satisfactory quantity of amino acids for nitrogen metabolism and may at times produce serious febrile reactions in patients in the acute phases of hepatitis. We have the clinical impression that they may be harmful to a very acutely damaged liver. Intravenous hypertonic dextrose remains a very efficient means of augmenting total caloric intake and, if the patient's cardiovascular system is unimpaired, may be run in with relative rapidity without an important increase in blood volume or in renal glycosuria.

Most of the present widely advocated commercial protein substitutes or supplements for oral administration are unpalatable and expensive. Many of them produce annoying flatulence, eructation, anorexia and diarrhea and therefore cannot be taken in large enough quantities to be worth while, their use may actually impair the total caloric intake. In the majority of instances, they have little merit over skim milk powder which has the advantage of being more palatable, more easily usable and much less expensive.

Lipotropic Agents.—The importance of the physiologic role played by various lipotropic agents has but recently been recognized. In the past few years the propaganda for the use of such agents as choline and inositol as supplements in the treatment of cirrhosis has been tremendous. One of these agents is no doubt a very necessary addition to the purified diets of growing laboratory animals, but no actual evidence has been offered that such supplements to the amounts contained in an adequate, well-balanced diet are helpful to the patient with chronic hepatitis. The same holds true, we believe, for the sulfur-containing amino acids methionine and cystine. It is unlikely that a few pure agents of this sort can protect against the development of the acute, degenerative intrahepatic processes associated with "alcoholic cirrhosis." The liver takes an essential part in so many vital metabolic processes that the number of raw materials required for its health and activities must be myriad. It seems improbable, therefore, that the administration of a few pure compounds can result

in marked improvement in function in an already severely damaged liver

Vitamins—The popular demand for innumerable vitamin supplements deserves, in our experience, a similar skepticism. If definite, suggestive signs of vitamin deficiency exist, the inclusion of that particular vitamin in the regimen is indicated, but no conclusive evidence has been presented that vitamin deficiency plays an important role in the development of chronic intrahepatic disease or that the addition of vitamins to the amounts contained in a full well-balanced diet is desirable. It is even possible that in the presence of severe liver disease certain vitamins are poorly utilized. When the blood prothrombin concentration is low, supplements of vitamin K-active compounds should be provided, but it is improbable that a damaged liver is any more likely to synthesize prothrombin if huge amounts, rather than a few milligrams daily of vitamin K are given.

MANAGEMENT OF EDEMA

The management of the edema of chronic or subacute liver disease is still a difficult problem, but nowadays it may be attacked by the additional aids of a more strenuous restriction of sodium and of the administration of human albumin.⁴ A fundamental means of limiting the accumulation of edema fluid is deprivation of the sodium required for its production. In this respect the present day "low sodium" diets are much more efficient than were the relatively ineffective "low salt" diets of the past. If sodium intake is adequately limited, fluid intake will not require more than moderate limitation. Fanaticism for sodium restriction should not, however, be carried to the point where the daily calorie intake is seriously impaired by the extreme unpalatability of the diet. Certain salt substitutes such as potassium and ammonium chloride may obviate this difficulty. It should be remembered, moreover, that unless renal tubular function is normal such a rigid fixed base restriction may produce acidosis. Mercurial diuretics are often effective, particularly if a mild acidosis has first been produced by the administration of ammonium chloride. The latter drug is best given in the form of enteric-coated tablets to avoid gastric irritation.

If the serum albumin is below 3 gm per 100 cc, a course of intravenous human albumin (50 gm daily for seven days), by increasing blood osmotic pressure, usually causes a very satisfactory diuresis. At the present time this valuable supplement is unfortunately not generally available. Mercurial diuretics are usually more effective if blood osmotic pressure is normal.

Despite all these measures, the fluid retention associated with a severely damaged liver may persist. That prolonged and copious administration of crude liver extract may produce diuresis and improve other hepatic functions has been suggested, but no critical data to

prove this hypothesis have yet been presented by its advocates. When possible, abdominal paracenteses are to be avoided because of the attendant loss of albumin with resulting depletion of the protein reserves.

BED REST

In the acute exacerbations of chronic hepatitis, prolonged, complete bed rest is essential for lowering the general metabolic demands upon the liver. Even for the patient in a histologically stationary stage of the disease, when fibrosis and repair have occurred, restriction of physical activity and strict avoidance of fatigue are very important.

LATE STAGE COMPLICATIONS

Portal hypertension with esophageal varices is a serious mechanical complication of the late stages of chronic hepatitis. All patients with known intrahepatic fibrosis should be examined periodically by x-ray to determine the possible development of this hazard. To date, the most promising solution of this problem of portal hypertension is the recently revived surgical formation of a permanent, artificial venous shunt between the portal and caval venous circuits.¹ Because the severing of the portal blood supply to the liver in the establishment of a true Eck fistula, as has been advocated by some surgeons, is physiologically unsound, other sites of venous anastomosis should be chosen. Whether these circulatory shunts will stay patent for long periods of time or whether their diameters are sufficient to provide an adequate decompression of the portal hypertension remains to be proved by time and by the follow-up of patients subjected to these operations.

ILLUSTRATIVE CASES

In order to illustrate the therapeutic points that have been discussed, the following cases are presented. In addition to careful clinical and laboratory observations, needle aspiration liver biopsy was carried out in each case and, as will be noted, the histologic information furnished by it formed an excellent basis for making decisions as to treatment.

CASE I.—A 47 year old man entered the hospital because of fatigue, anorexia and abdominal pain of four months' duration.

One year previously a positive reaction to a Hinton blood test had been accidentally found. No clinical history or physical manifestations of syphilis were discovered. Spinal fluid examination was normal. Antiluetic therapy of bismuth and mapharsen was started. At the beginning of the second course of mapharsen therapy, ninety days after the completion of the first course, the patient complained of anorexia and fatigue. There was a weight loss of 20 pounds during the next six weeks, at the end of which time jaundice first appeared. Mild icterus waxed and waned during the three months before hospitalization.

Physical examination on admission showed a well nourished, moderately jaundiced man with an enlarged, tender liver and a palpable spleen. No edema, ascites

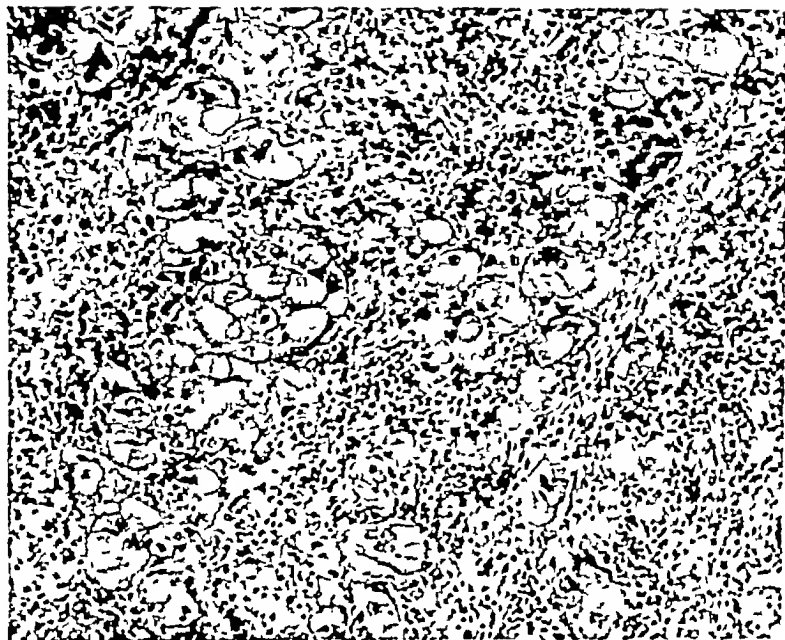


Fig 164 (Case I) --Biopsy at hospital admission



Fig 165 (Case I) --Biopsy nine months after that of Figure 164

or spider angiomas were evident. A needle aspiration liver biopsy was described as follows "The biopsy shows many small clusters of abnormal liver cells imbedded in large amounts of fibrous tissue. The liver cells are markedly swollen with an hydropic type of vacuolization. Some of these contain small acidophilic spherules suggestive of those seen in the late stages of infectious hepatitis. The connective tissue shows a rather marked mononuclear infiltration with lymphocytes predominating. There is moderate bile duct proliferation" (Fig 164)

Because of the acute inflammatory phase present, this patient was maintained on strict bed rest under close hospital observation for five weeks, although symptoms were absent after the first two weeks. He received a 2400 caloric diet, containing 120 gm of protein, and daily intravenous dextrose supplements. At the conclusion of this period there had been no change in the physical examination, laboratory hepatic function tests or biopsy histology. He was discharged home to follow a strict regimen of bed rest and high caloric diet. Four months later the icterus had finally disappeared and liver function had improved. The patient gradually returned to a full-time working schedule.

One year after the onset of jaundice the patient was pursuing a fairly normal life, adhering to a regular daily program with high caloric diet, ten hours of sleep and the avoidance of alcohol and physical fatigue. Physical examination showed no jaundice, fluid retention or spider angiomas. The liver and spleen were both enlarged, they had not changed in size since hospital entry. A barium swallow demonstrated no esophageal varices. Except for the cephalin flocculation, all hepatic function tests had returned to normal. The histologic report of a needle liver biopsy obtained at this time was "The biopsy shows marked improvement in comparison with the preceding one. The nodules of regeneration are larger and the intervening fibrous tissue less. The liver cells appear completely normal. In the fibrous bands small numbers of lymphocytes are still present, and bile ductules are fairly numerous. The findings indicate a definite inactive cirrhosis" (Fig 165)

COMPARATIVE STUDIES*

	Serum Bilirubin	Prothrombin Time	Total Protein	Albumin	Globulin	Ceph Flocc.	Bromsulfalein 5 mg
Hospital admission	2 3/3 2	30	6 36				
Hospital discharge	2 2/2 5	27	6 13	2 47	3 89	3+/4+	40%
9 mo after discharge	Normal	24	7 90	2 62 5 20	3 51 2 70	3+/4+ 2+/3+	40% <5%

* The following applies to "Comparative Studies" in all five cases
 Liver size—distance in cm of right lobe below costal margin in deep inspiration
 Serum bilirubin—mg per 100 cc direct/indirect
 Prothrombin time—seconds normal control 20 seconds
 Serum total protein—gm. per 100 cc.
 Serum albumin—gm per 100 cc.
 Serum globulin—gm per 100 cc
 Cephalin cholesterol flocculation—readings 24 hr /48 hr
 Bromsulfalein—5 mg/kg dose, sample in 45 minutes, or 2 mg/kg dose sample in 30 minutes

Comment—Subacute, diffuse inflammatory disease of the liver usually does not improve rapidly. A prolonged, strict convalescence over a period of many months is ordinarily required for healing. As in this case, the patient and the physician may be rewarded eventually by sufficient parenchymal cell regeneration to allow normal activities and improved laboratory function tests. The clinical and pathologic pictures were compatible with either "arsenical" hepatitis or serum hepatitis. Considerable evidence has accumulated to prove that pro-

longed "arsenical," serum or epidemic infectious hepatitis may result in disordered architecture of the liver with fibrosis. This sequence of events occurred in this patient to produce a so-called compensated cirrhosis.

CASE II—This 41 year old housewife was admitted to the hospital when she could no longer rise from her bed because of severe peripheral polyneuritis.

For fifteen years she had taken a considerable amount of alcohol, particularly during the two years preceding admission. For the past two years her diet had been low in protein, and she had had frequent episodes of nausea and vomiting associated with upper abdominal pain but with no icterus. Ankle edema, abdominal distention and orthopnea were present periodically and for these symp-

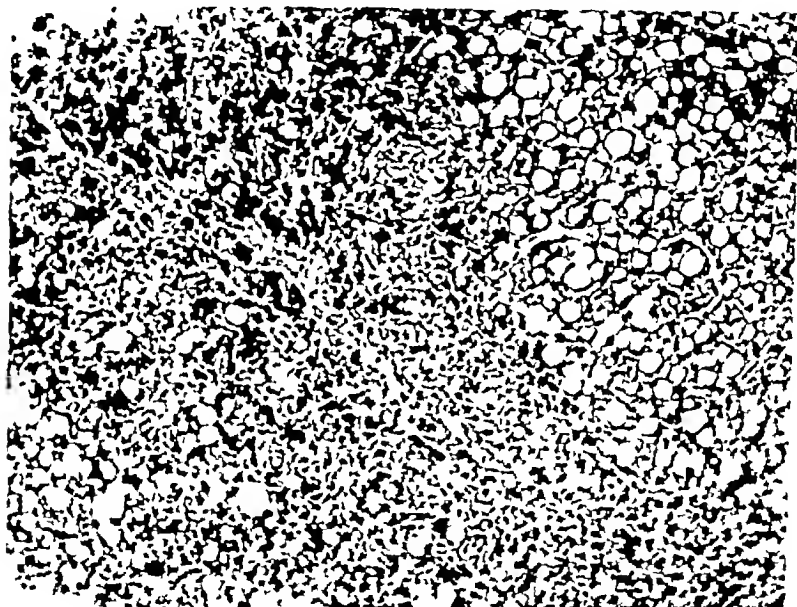


Fig 166 (Case II) —Biopsy on first hospital entry

toms she had been digitalized without benefit on three separate occasions. For one year her memory had been failing. For five months before hospital entry she had had increasingly severe symptoms of a polyneuritis with numbness and tingling of all four extremities followed by wrist drop and weakness of the legs. During the two weeks before admission she lay in bed almost completely helpless.

Physical examination showed an obese, drowsy, confused, confabulating woman who was very slightly icteric. Her tongue was red and smooth. A severe peripheral neuritis with bilateral wrist and toe drop was present, reflexes were absent. The liver was huge and slightly tender. The spleen was enlarged. There were numerous spider angiomas but no ascites or peripheral edema. The temperature was 101° F., white count 11,600 with 80 per cent of polymorphonuclears and hemoglobin was 10.3 gm per 100 cc.

A needle liver biopsy, obtained one week after admission was described as follows: "The liver cells are swollen and granular. Many polymorphonuclear leuko-

cytes are scattered throughout the section. There is extensive fatty infiltration. Questionable "alcoholic" hyalin is seen. Some fibrosis is already present. The biopsy is consistent with acute "alcoholic cirrhosis" (Fig 166).

For seven weeks this patient was treated with bed rest, a 2800 caloric diet high in carbohydrate and protein and low in fat, and many supplements including liver extract, vitamins, brewer's yeast powder, inositol and choline. To guarantee adequate caloric intake, daily tube and intravenous feedings were given during the first ten days. At the end of seven weeks the patient was mentally alert and had a good appetite. The wrist drop had disappeared and the tongue had returned to normal. Icterus had disappeared and the liver had decreased somewhat in size. The report of a liver biopsy obtained at that time was "There are still a few small groups of polymorphonuclears in the parenchyma, but the majority of the hepatic cells now appear normal. There is considerably less fatty infiltra-



Fig 167 (Case II) —Biopsy seven weeks after that of Figure 166

tion as compared to the original biopsy. There is a slight increase in fibrous tissue" (Fig 167).

After discharge from the hospital this patient was followed at monthly intervals in the Outpatient Clinic. She ate more fat and considerably less protein than was advised. With the aid of braces, she slowly became ambulatory. Throughout the following year she continued to take faithfully the prescribed supplements—choline chloride, 3 gm, 2 polyvitamin capsules and 30 gm of brewer's yeast powder daily. (This fact was confirmed by all the members of her family.) Despite this strict adherence to prescribed medications, her liver doubled in size during the latter six months of the year and in the last two months ascites and peripheral edema reappeared. For six weeks before readmission, 6 gm of choline chloride daily, in addition to the other adjuvants, were taken. Confidential information from a member of the family confirmed the suspicion that for five months the patient had been consuming an unknown quantity of alcohol.

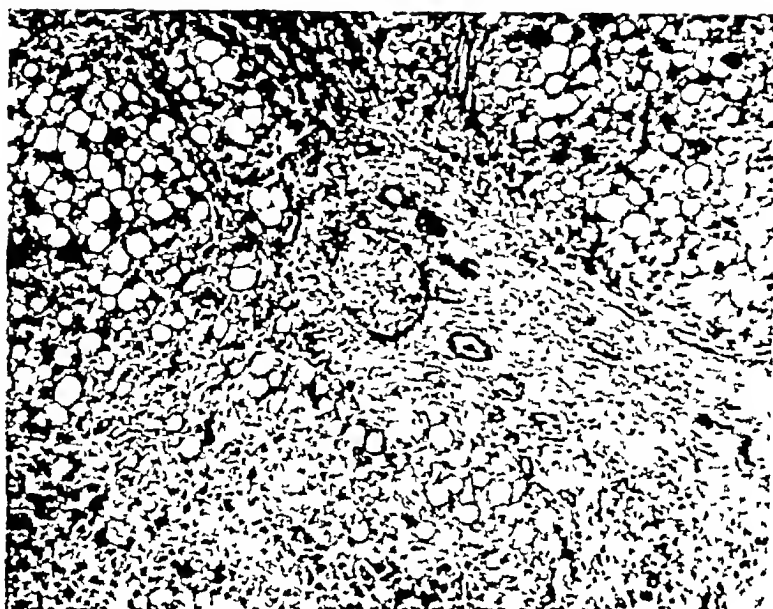


Fig 168 (Case II) —Biopsy at second hospital admission

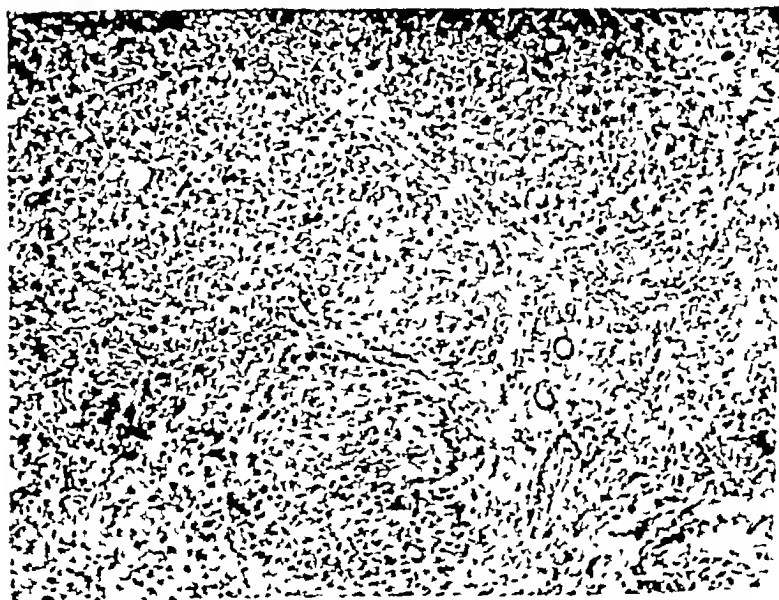


Fig 169 (Case II) —Biopsy four weeks after that of Figure 168

Physical examination on re-entry showed an obese, nonjaundiced woman in no distress. Although reflexes were absent and vibration sense was markedly diminished, she had recovered full use of her extremities. The spider angiomas were increased in number but the tongue had remained normal. Slight ascites and marked peripheral edema were present. The nontender liver was larger than on the first admission, the spleen seemed somewhat larger.

A liver biopsy, except for the increase in fibrous tissue, resembled the original one. "The bands of connective tissue are wide and exceptionally dense. They show moderate inflammatory infiltration. There is marked reduplication of small bile ducts. The islands of liver cells show severe fat vacuolization, suggestions of 'alcoholic' hyalin, and numerous focal neuroses" (Fig 168).

The patient was treated with a 2400 caloric, high protein, low fat diet with no supplements. During the next four weeks the liver decreased in size and ascites disappeared. Liver function tests showed improvement. A biopsy taken at the end of this period of treatment showed "The fat has entirely disappeared from the liver cells and the focal necroses and acute inflammatory changes noted in the previous biopsy are no longer seen. The degree of fibrosis has not appreciably altered" (Fig 169).

COMPARATIVE STUDIES

	Liver Size	Serum Bilirubin	Total Protein	Albumin	Globulin	Ceph. Flocc.	Bromsulphalein 5 mg
Hospital entry	16	2.0/3.0	6.8	3.4	3.4	0/0	25%
Hospital discharge	12	Normal	7.8	4.6	3.2	1+/2+	0
Second admission	26	Normal	6.8	3.7	3.1	2+/3+	35%
Second discharge	16	Normal	7.2	5.2	2.0	2+/3+	24%

Comment—In this patient it is clear that the regular administration of vitamins and a lipotropic agent did not prevent the return of fatty infiltration and acute inflammatory degeneration caused by poor diet and alcoholism. It is also clear that the rate and degree of histologic repair was approximately the same when the patient was treated with diet alone as when she was treated with diet plus multiple supplements.

CASE III—A 39 year old bartender entered the hospital because of jaundice and marked ascites.

For many years he had consumed large quantities of alcohol. Six years before entry, because of the development of a severe alcoholic tremor, he temporarily gave up drinking. A year before he was admitted to the hospital he returned to his former alcoholic habits and began to work sixteen out of twenty-four hours and to eat irregularly. Two weeks before entry he noted the rapid onset of painless jaundice, ascites and edema of the legs.

Physical examination revealed a moderately jaundiced, well nourished man with a huge ascites and marked sacral and leg edema. The tongue was normal and there was no spider angiomas and no signs of polyneuritis. After paracentesis an enlarged liver and spleen were palpable. A needle liver biopsy report stated "The biopsy shows moderately severe cirrhosis, marked infiltration, considerable bile stasis, marked degenerative changes in the liver cells, including 'alcoholic' hyalin, many focal necroses and considerable polymorphonuclear infiltration" (Fig 170).

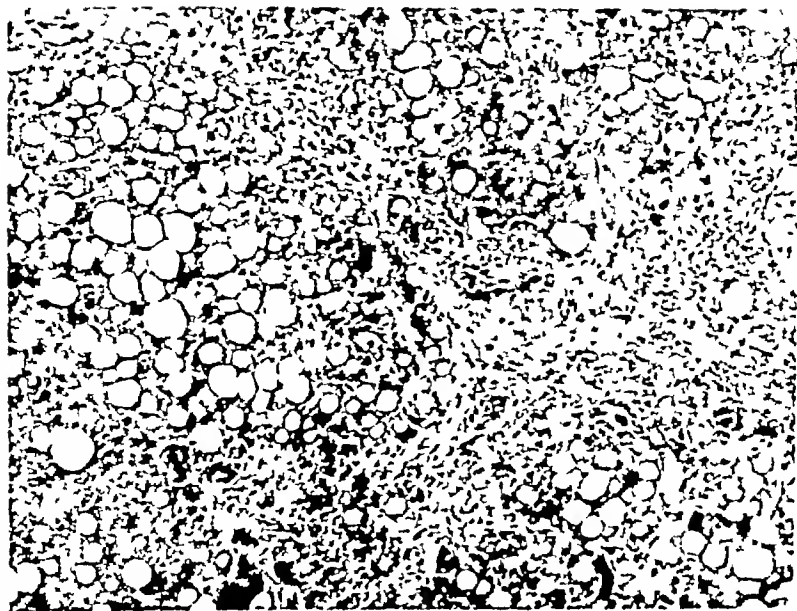


Fig 170 —(Case III) —Biopsy at hospital entry

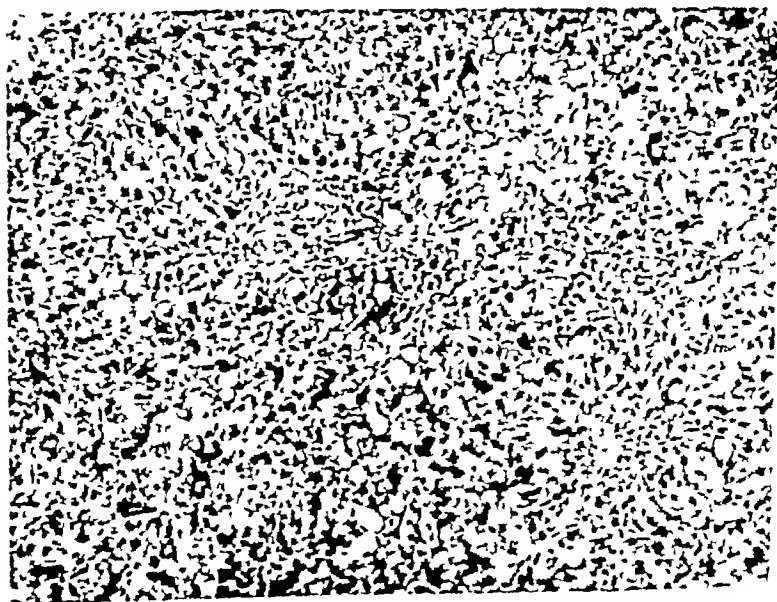


Fig 171 (Case III) —Biopsy four weeks after that of Figure 170

ous hemangiomas are satisfactorily treated with sclerosing solutions such as sodium morrhuate. Many varieties require surgery either alone or in combination with irradiation either by x-ray or radium. Plastic surgery is frequently necessary in extensive disfiguring lesions. Osseous hemangiomas have responded to x-ray therapy (Kaplan⁶).

It is well known that irradiation to growing bones may produce permanent shortening of an extremity and disfigurement. The use of irradiation about the orbit may cause disturbances of the crystalline lens, if applied near tooth buds, defective dentition may result. Radiation changes in the skin some years after treatment are also occasionally observed. Such sequelae may have to be risked if the nature of

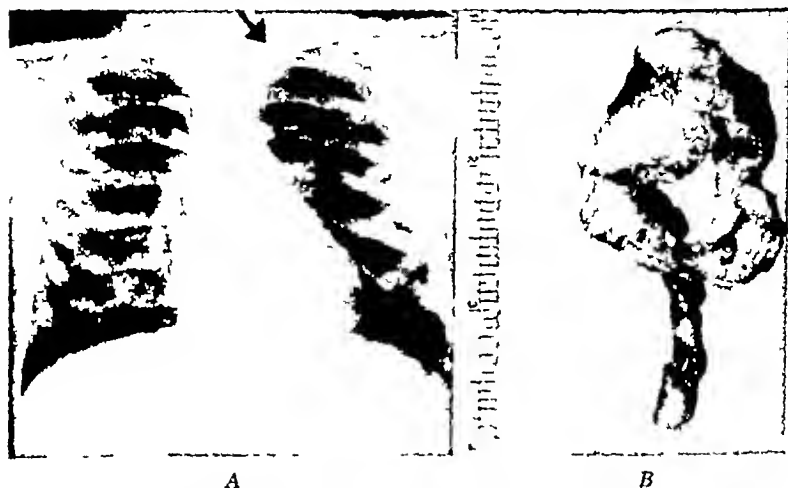


Fig 67—Neurofibromatosis (C. D., female, aged 6 years). Child shows many changes associated with von Recklinghausen's disease— café-au-lait spots, nevi, hypertelorism. Roentgenogram of thorax (A) shows a mass in left upper thorax producing a convex shadow. At operation a plexiform neuroma (B) 4 inches in its greatest length was found.

the lesion requires irradiation. These possibilities should be thoroughly understood by all concerned before such therapy is instituted.

Lymphangioma—This tumor of early life may appear as (a) a bleblike cyst on the skin or mucosal surface, (b) an infiltrating soft mass in the deeper tissues, or (c) a multiloculated cystic lesion about the head, neck or thorax.

TREATMENT is by surgery or cauterization, rarely by irradiation. The use of sclerosing solutions may prove satisfactory in some cases.

Nevus.—This pigmented tumor varies from the small, flat nevus to the large "bathing trunk" variety, the hairy nevus, and the blue-black melanoma. Nevi are diagnosed without difficulty and the following

This patient was treated in the hospital for six weeks with absolute bed rest and a daily diet of 3000 calories, low in sodium content and containing 160 gm. each of protein and fat. He was given no vitamin or lipotropic supplements. Four gm of enteric-coated ammonium chloride were administered daily and 2 cc. of mercurhydrin intravenously on alternate days.

The jaundice slowly subsided to a minimal degree at the time of discharge from the hospital. The liver decreased in size. Fluid retention remained a problem during the greater part of his stay but required tapping only twice and by the time he was discharged was barely detectable. His appetite gradually improved and he felt well. He continued on a similar regimen at home and follow-up examinations in the Outpatient Clinic showed a steady improvement. A needle liver biopsy was obtained four weeks after the first one. "The degree of fat vacuolization has decreased markedly though some still persists. The liver cells are frequently swollen and multinucleated, and the nucleoli seem very large and prominent. There is still an occasional focus of necrosis with polymorphonuclear infiltration. There is considerable bile pigmentation of liver cells, Kupfer cells and an occasional dilated bile canaliculus. There has been no change in the fibrous tissue of the portal areas" (Fig 171).

COMPARATIVE STUDIES

	Liver Size	Serum Bilirubin	Total Protein	Albumin	Globulin	Bromsulfalein 2 mg
Hospital admission	14	16 7/23 0	4 74	2 06	2 68	60%
Hospital discharge	5	2 8/3 4	5 52	2 78	2 74	15%
1 month after discharge	3	0 8/0 9	6 78	4 36	2 42	

Comment—This patient, who was gravely ill from an acute inflammatory degenerative hepatitis, responded as well clinically and histologically to a regimen of absolute bed rest and a high protein, high fat diet *without* vitamin or lipotropic supplements as have other patients with similar initial histopathology who were treated with a low fat diet and multiple supplements. Further such observations will be necessary before an accurate comparison of various therapeutic regimens can be made.

CASE IV—This 30 year old housewife entered the hospital for diagnosis of the cause of marked abdominal distention of five weeks' duration.

For four years her dietary intake had been increasingly inadequate as the result of a steady alcohol consumption. Two years before entry it was apparent to her that she had lost considerable weight, she was anorexic, weak, constantly tired and becoming more and more irritable. Four months before admission she developed repeated attacks of vomiting after meals, two months later jaundice was first noted. During the five weeks immediately preceding hospitalization, she gained 12 pounds in weight although she ate very little and had repeated attacks of severe upper abdominal pain.

Physical examination showed a very nervous, thin woman with moderate jaundice, a tense abdomen containing a considerable ascites and a very large, exquisitely tender liver. Peripheral edema of moderate degree, spider angiomas, "liver palms" and a red smooth tongue were evident. She had a temperature of 101°, a white count of 14,000 with 90 per cent polymorphonuclear leukocytes, and a hemoglobin of 9.5 gm per 100 cc. A needle liver biopsy was reported as follows: "The liver

shows a diffuse cirrhotic process with obliteration of the lobular architecture and a diffuse inflammatory reaction which involves the lobules as well as the periportal connective tissues and shows a high proportion of polymorphonuclear leukocytes. Fat vacuolization is moderate in amount. The liver cells show suggestive 'alcoholic' hyalin and there are numerous focal necroses' (Fig. 172).

This patient was hospitalized for five weeks. In spite of constant protest, she was made to eat an average of 2200 calories daily including 130 gm. of protein. This was supplemented with intravenous administration of hypertonic dextrose and whole blood transfusions. Because of the existing signs of vitamin deficiency, vitamin supplements were added. The administration of oral casein hydrolysates or yeast powder consistently resulted in diarrhea and further anorexia, these supplements were therefore omitted. Despite the fact that the diet was kept low in sodium content, the severe edema could not be adequately controlled even with the addi-

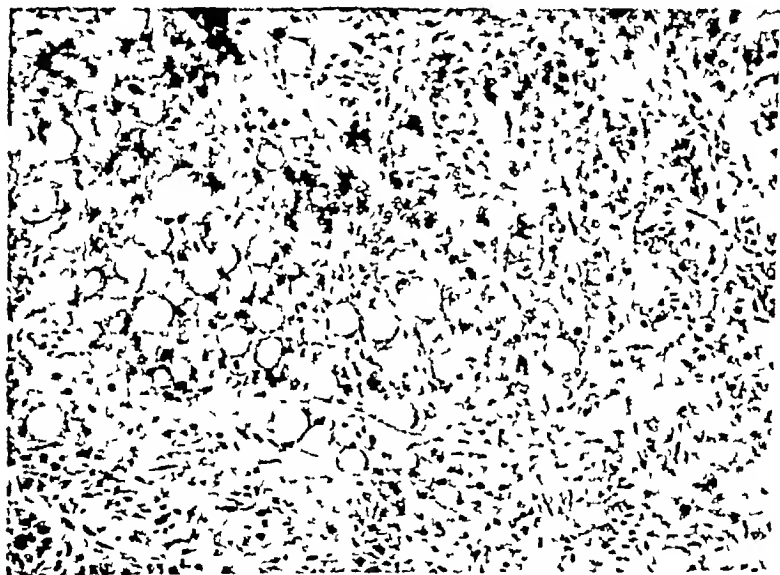


Fig. 172 (Case IV) —Biopsy at hospital admission

tion of 4 gm. of enteric-coated ammonium chloride daily and 2 cc. of mercurhydrin given intravenously on alternate days. She was therefore given 50 gm. of human albumin intravenously daily for seven days. A marked diuresis promptly occurred during which she lost 17 pounds of weight in two weeks. A twenty-four hour urine, collected during this period, contained 114 gm. of chloride (as sodium chloride) as compared to a daily total oral intake of 45 gm. of chloride (as sodium chloride and including ammonium chloride supplements). The serum albumin concentration was raised to 5 gm. per 100 cc. Hepatic albumin synthesis became adequate to maintain this level. At the time of discharge from the hospital the liver was still very large but no longer tender, very slight icterus remained but there was no fluid retention.

The patient continued at home with semibed rest and a high-calorie diet. When seen three months later, her liver was nontender, somewhat smaller and very firm. There was no abnormal fluid retention but there was still very slight icterus. Her

appetite was excellent and her strength greatly increased. Laboratory hepatic function tests had improved. Biopsy of the liver showed "In comparison with the first biopsy the present specimen shows less fat, no hyalin, no foci of necrosis, but considerably more fibrosis. Islands of regeneration are uniformly small" (Fig 173)



Fig 173 (Case IV) —Biopsy three months after that of Figure 172

COMPARATIVE STUDIES

	Liver Size	Serum Bilirubin	Total Protein	Albumin	Globulin	Bromsulfalein 2 mg
Hospital admission	16	5 2/7 1	4 95	2 47	2 48	
Hospital discharge	11	1 0/1 8	7 70	5 0	2 70	15%
3 months after discharge	10	0 8/1 4	7 8	5 3	2 5	10%

Comment—Fever, polymorphonuclear leukocytosis, and abdominal pain are often found with acute exacerbations of so-called alcoholic cirrhosis. Even when considerable hepatic fibrosis and architectural change have occurred, strenuous and prolonged treatment of such exacerbations of the degenerative process is worthwhile and may result in sufficient reparative regeneration of hepatic parenchyma to allow the patient moderate daily activity with comfort. Where fluid retention associated with a low serum albumin causes great discomfort, the diuresis following the administration of human albumin may tide the patient over a critical period, allow an increase in caloric intake by removing ascites, and may possibly even improve liver function through removal of interstitial hepatic edema fluid.

CASE V—This 39 year old housewife entered the hospital in 1938 because of abnormal menstrual bleeding

Since the age of 9 years she had taken a glass of wine daily. Her diet had always been high in fat and moderately low in protein. A very large liver and the tip of the spleen were palpable although repeated bromsulfalein tests (2 mg) were normal. A barium swallow showed no varices. A peritoneoscopy demonstrated a finely granular cirrhotic liver. In 1939 a hysterectomy was performed, and a liver biopsy secured at the time of operation was described as follows: "The liver shows a severe and evidently long-standing cirrhotic process with large bands of scar tissue densely infiltrated with lymphocytes and occasional polymorphonuclear leukocytes surrounding islands of liver cells devoid of lobular architecture. The liver cells show extensive fat vacuolization, and a moderate number of them contain 'alcoholic' hyaline" (Fig 174). No dietary suggestions and no medications

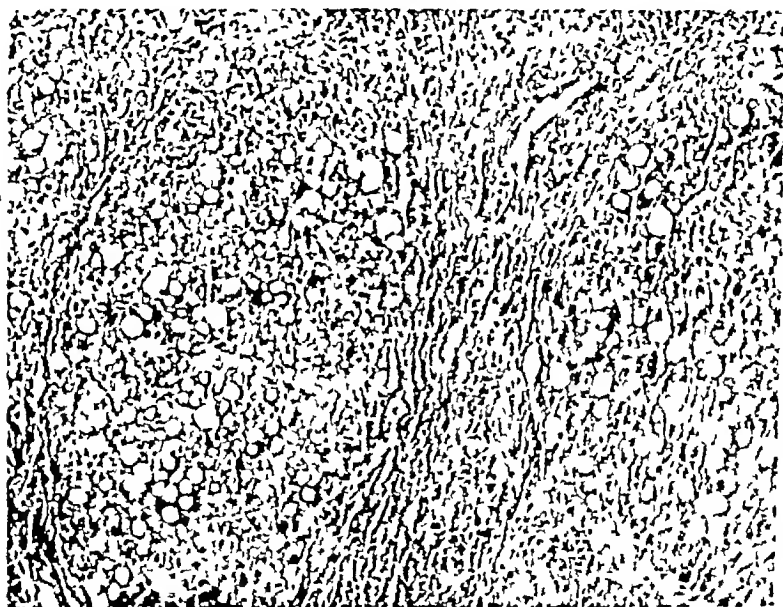


Fig 174 (Case V)—Biopsy in 1939

were given to the patient at this time but she was instructed to omit her wine intake.

In January 1943 she reported to the Outpatient Clinic with mild jaundice. Except for this and a slight decrease in liver size, physical examination had not altered. She was instructed in a high carbohydrate, high vitamin diet, but, as previously, no suggestions were made as to the limitation of physical activities. The icterus disappeared in six weeks.

In December 1944 a massive hematemesis occurred following which she was hospitalized. There had been no further change in the size of the liver. A barium swallow demonstrated esophageal varices. Laboratory tests showed 10 per cent bromsulfalein retention in forty-five minutes after an intravenous dose of 5 mg; a prothrombin time of twenty-four seconds; a total serum protein of 7.5 gm per 100 cc with serum albumin of 4.11 gm and globulin of 3.39 gm; cephalin floccu-

lation 0/1+ The patient was instructed in a mechanically soft 3500 caloric, high protein diet.

Three months later splenectomy, left nephrectomy and left renal-splenic vein anastomosis were performed by Dr Richard H Sweet. A liver biopsy taken during this operation was described as follows "The liver shows large lobules separated by fine bands of connective tissue in which there are a few bile ducts and chronic inflammatory cells The hepatic veins no longer occupy the center of these lobules but are found in varying positions"

The patient has remained fully ambulatory and asymptomatic since this procedure There has been no further gastrointestinal bleeding and no change in the size of the liver or in the laboratory hepatic function tests She has continued to follow a careful mechanically soft diet high in calories and in protein.

Roentgenologic re-examinations in September 1945 and in November 1946 showed no change in the size and extent of the esophageal varices as compared with the examination made in February 1945 The findings of an esophagoscopy performed in February 1946 by Dr E B Benedict were described as follows "The upper esophagus was normal At a point about 31 cm from the upper teeth, or approximately 14 cm above the cardia, there were several folds in the mucosa which had the appearance of pale, sclerosed or empty varices The needle was introduced in two places but no blood could be obtained."

Comment—Because of the severe fibrosis noted in the first liver biopsy, it is improbable that a proper, strict dietary regimen with moderate curtailment of physical activity applied at that time would have prevented the subsequent serious portal hypertension These directions should, nevertheless, have been given, strict adherence to them should have arrested earlier the degenerative hepatic process and prevented the acute exacerbation in 1943 Sufficient hepatic parenchymal cell regeneration did occur to allow a normal daily life and to provide little evidence of functional derangement by laboratory tests Therefore, in 1944 after the hematemesis, primary therapeutic consideration could be placed upon the portal hypertension An annual esophagoscopy is planned If patent varices appear, these will then be injected with sclerosing agents under direct vision through the esophagoscope

SUMMARY

Recent trends in the treatment of subacute and chronic hepatitis have been discussed Five illustrative cases have been presented in detail The foundations of successful therapy for this group of diseases remain today as a decade ago (1) the administration of high caloric, well balanced diet and (2) the restriction of physical activity ✓

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CLINICAL MANAGEMENT OF EDEMA IN BRIGHT'S DISEASE

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EDEMA often proves to be a serious and incapacitating complication in patients with acute nephritis as well as in those suffering from the "nephrotic syndrome" and the terminal stages of chronic Bright's disease. It is readily apparent that generalized edema adds to the discomfort of the patient, often interferes with appetite and digestion, may predispose to infections, and more particularly, may increase cardiac and renal failure as a consequence of interstitial edema of these organs. In certain stages of the disease, generalized edema may prove to be the chief cause of prolonged invalidism. In the absence of a specific therapeutic approach to the underlying renal lesion, it is useful to attempt to correct this distressing manifestation of the disease.

The principal causes of edema in patients with Bright's disease appear to be (a) decreased ability on the part of the kidney to excrete sodium, chloride and water, (b) disturbance in protein metabolism characterized by proteinemia, hypoalbuminemia and hyperglobulinemia, and (c) cardiac failure. It is obvious that the choice of therapy will be determined in large measure by the predominant type of physiological disturbance. The effectiveness of therapy will parallel one's ability to correct or improve the underlying abnormality responsible for edema. It is important to emphasize the fact that disappearance of edema does not necessarily imply improvement in the basic disease of the kidney. It is now well recognized that many patients with the nephrotic syndrome may lose all evidence of edema for periods of one or more years, although in most of these patients some degree of proteinuria persists and the underlying nephritis progresses to terminal uremia. The temporary nature of this clinical improvement which accompanies a diuresis and loss of edema is difficult for both patient and physician to admit and appreciate. For an excellent description of the natural history of Bright's disease one should consult the Croonian Lectures given by Ellis in 1942.¹

Sodium Content of the Diet.—Of prime importance in the management of edema is the restriction of sodium intake. Impairment of kid-

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ney function is usually associated with an inability to excrete sodium, chloride and water at a normal rate (Fig 175) Of these changes the decreased excretion of sodium is the essential defect, since it has been demonstrated repeatedly that the administration of chlorides, other than sodium chloride, does not induce water retention and that fluid administration in the presence of a low sodium intake does not aggravate edema²

Most of the sodium in an average hospital diet is present in the form of sodium chloride, a major portion of which is added to the

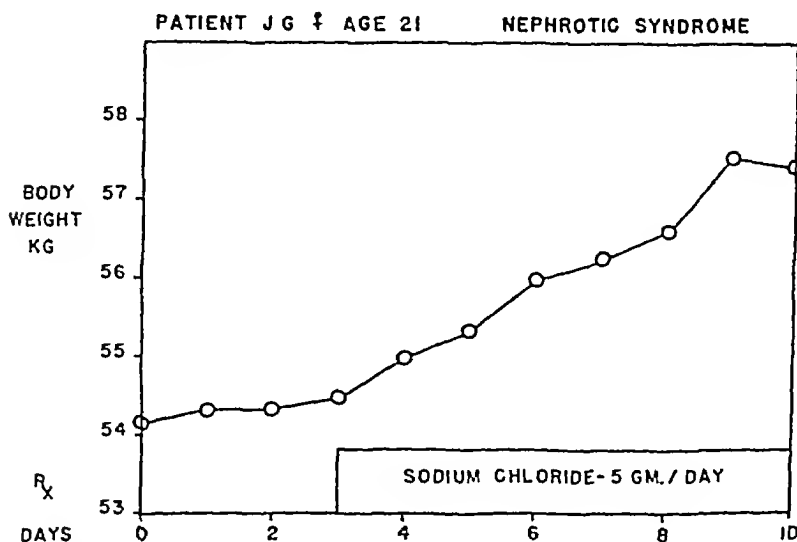


Fig 175—Patient J G, a woman aged twenty-one, had severe nephrotic syndrome with moderate nitrogen retention and slight hypertension. Addition of 5 gm of salt per day in her basic low salt regimen was followed by a rapid gain in weight which reflected the complete retention of the additional sodium.

food in its preparation and at the table. A diet containing less than 5 gm of sodium (expressed as sodium chloride) may be obtained by omitting salty foods such as ham, olives and the like, by restricting the quantity of salt used in cooking and by eliminating the addition of salt at the table. This degree of salt restriction is effective, however, in controlling the edema only in those patients accustomed to ingesting excessive quantities of salt. For most patients, it will be necessary to restrict the sodium chloride intake to less than 1 gm daily and occasionally to less than 0.5 gm daily. To prepare such a low salt diet it is necessary to eliminate the use of sodium chloride in the preparation of food, to reboil vegetables after discarding the initial water, to use salt-poor bread and sweet butter, and to avoid

all foods of high salt content To improve palatability the authors recommend the use of salt substitutes such as Neo-Curtasal * *Eka Salt, which is available commercially, should never be employed* for these purposes, since it contains large quantities of sodium, although it is essentially chloride-free Thus the intake of the essential offending ion (sodium) remains high when using this preparation, and one might just as well use ordinary table salt!

With patients on a low sodium regimen the physician must also be on the alert to eliminate the inadvertent administration of medications which contain appreciable quantities of sodium (sodium bicarbonate, sippy powders, triple bromides, sodium lactate, sodium acid phosphate, sodium salicylate and sodium thiocyanate) With the precautions employed in preparing a low salt diet, care should be taken to provide supplementary vitamins and minerals It is customary to give twice the minimal daily requirement of vitamins recommended by the National Research Council In patients who ingest moderate quantities of milk it is not necessary to supplement the intake of calcium When indicated, calcium lactate or gluconate may be given, however Protein deficiency may be prevented even though the diet is restricted in its protein content by administering a diet of high caloric value consisting principally of carbohydrate and fat

✓ In female patients with edema, it is well to consider the phase of ovarian or menstrual cycle in estimating the effectiveness of any given diuretic agent It is much more difficult to induce a sodium diuresis during the premenstrual period than it is immediately following the onset of menstruation³

Acid Ash Diet, Acidifying Salts and Potassium Medication.—Considerable benefit to patients with edema may be obtained from a diet of acid ash residue The effectiveness of this regimen depends upon the necessity for excreting base with fixed acid derived from the diet The most readily available source of fixed base is sodium, and the excretion of sodium with the acid residue of the diet will result in a decrease in extracellular fluid

The effectiveness of an acid ash diet may be enhanced by the supplementary administration of ammonium chloride Again the mechanism of reducing extracellular fluid is accomplished by the necessity for increasing the excretion of fixed base *Ammonium chloride should not be administered to patients with renal acidosis and uremia*

Potassium salts also may act as mild diuretic agents Most observers agree that in the diuresis induced by potassium salts sodium is swept out Potassium salts should not be administered to patients with severely impaired renal function, as toxic levels of serum potassium may be attained⁴

* The authors are indebted to Mr Shepherd M Crain of the Winthrop Chemical Company for a supply of Neo-Curtasal.

The restriction of water is not indicated in patients with edema who follow a low sodium diet. Most patients will restrict fluids spontaneously because of the lack of salt in the diet. Schemm² has recommended a regimen for patients with edema which consists of the administration of large quantities of fluid when the dietary sodium is restricted to 0.5 gm per day. An acid ash diet and the administration of ammonium chloride under such circumstances are usually desirable. It is now generally accepted that fluid restriction is not necessary in the presence of adequately controlled sodium intake. The added usefulness of a fluid intake of at least 2500 to 3000 cc seems well established in patients with cardiac edema.⁵

It is obvious that in certain patients restriction of sodium with the administration of excessive fluids and acidifying salts may result in an excessive lowering of the sodium level in the blood and extracellular fluid. This complication is rare in patients with nephrotic edema, whereas it may be observed in patients with pyelonephritis and hypertensive cardiovascular renal disease.

Digitalis.—Although digitalis is of no value as a diuretic agent in patients with the nephrotic syndrome without cardiac failure, it may prove lifesaving for patients with cardiac failure secondary to acute glomerulonephritis. For this reason it is important to review its value and indications. Studies suggest that approximately 25 per cent of the patients who die with acute nephritis do so primarily because of acute cardiac failure.¹ This is understandable when one appreciates the tremendous burden which sudden renal shutdown and associated hypertension impose on the heart. Since the probabilities are high that most patients with acute nephritis will recover completely if they are able to survive the initial period of renal shutdown, it is all the more important to be certain that digitalis is administered in adequate quantities upon the first indication of heart failure.

From a practical viewpoint it is now possible to digitalize a patient within six hours by the administration of a single dose of 1.2 mg of digitoxin, either intramuscularly or orally, as described by Gold.⁶ Digitalization in association with sodium restriction is most efficacious in these patients (Fig 176). During the period of oliguria, fluid intake should be restricted to that required to maintain body weight. In patients without abnormal fluid loss (vomiting, diarrhea, high fever) *this rarely exceeds 1500 cc per twenty-four hours*. Most patients, unfortunately, are given excessive fluids during the anuric or oliguric period, and considerable harm may be done by inducing generalized edema as a consequence of overenthusiastic hydration. There is no evidence to indicate that a diuresis will occur under any circumstances until the initial inflammatory reaction in the kidney subsides.

Edema in the late stages of chronic glomerulonephritis is frequently associated with hypertension and cardiac failure. Under these cir-

should be removed (a) the nevus of the blue-black (melanoma) variety, (b) an enlarging nevus of any nature, (c) cosmetically disfiguring nevi, and (d) those located at a site subject to trauma

Subcutaneous Tumors of Soft Supporting Structures (*Neuroma, Myxoma, Lipoma, Fibroma, Myoma, etc*)—The subcutaneous



Fig 68—Neurogenic sarcoma (D M, female, aged 5 years) A small swelling was noticed beneath the child's left mandible at the age of 10 months This began to enlarge about one year before this photograph was taken She also showed numerous cafe-au-lait spots

tumor frequently appears as a deceptively innocuous "bump" It may be present at birth and, of course, may involve any part of the body The skin is raised over it if the mass is located near the surface It is generally soft, but sometimes very hard, occasionally, when solid, it may feel cystic to the examiner The tumor is seldom tender and

cumstances digitalis is also indicated. In certain patients it may be difficult to differentiate nausea and vomiting following excessive digitalis administration and that due to acidosis and uremia.

Mercurial Diuretics.—Mercurial diuretics are a most effective means of mobilizing fluid in patients with *cardiac edema*. The use of these agents may augment greatly the effect of sodium restriction and digitalis administration. It is probable that the effectiveness of mercurial diuretics is dependent upon the accompanying increased sodium excretion. The authors favor the administration of mercury intramuscularly rather than intravenously and for this purpose employ prepa-

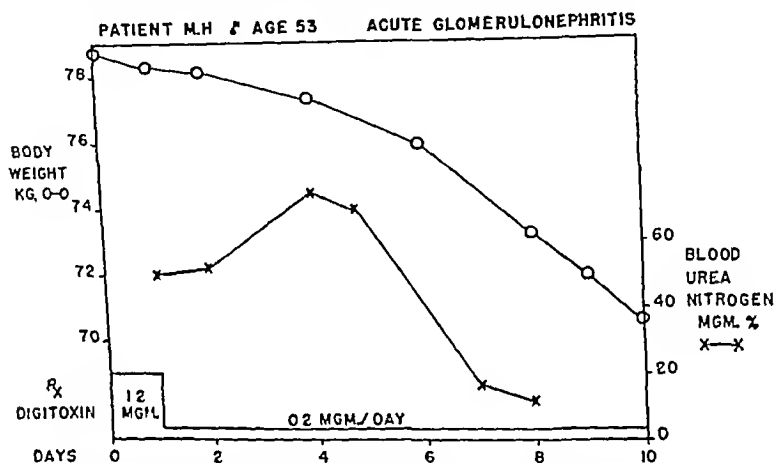


Fig 176—Patient M H, a man aged fifty-three, developed acute nephritis with dyspnea, headache, puffiness of face and slight generalized edema following exposure to toluene, the etiological nature of which is not established. Clinical course and urinary findings were typical of acute glomerulonephritis. The chart shows beginning weight loss after digitalization and while his blood urea nitrogen was still rising rapidly. There was a marked improvement in his cardiac symptoms and general clinical status and clearing of the chest as visualized by roentgenograms at the same time. Other therapy consisted of a very low sodium diet with 50 gm of protein, adequate calories, and 1500 cc of fluid per day.

rations such as Mercuhydrin*. It is probable that the use of divided doses of mercury throughout the twenty-four hours is a more effective and safer means of promoting a continued diuresis than the single administration of a large dose. Thus, 0.5 cc of Mercuhydrin every six hours may be preferable to 2 cc given as a single daily injection.

In the management of edema which is primarily the result of Bright's disease, there is a serious theoretical objection to the use of mercurial agents as diuretic substances. It is well known that excessive

*The authors are indebted to Dr C O Miller of the Lakeside Laboratories for the supply of Mercuhydrin.

doses of mercury result in renal damage, involving the renal tubules particularly. It is possible that small doses of organic mercurials administered parenterally may not produce permanent injury to the kidney tubules. This is difficult to establish, however, particularly in the presence of primary kidney disease. The authors feel that at the present time *mercurial administration is not justified in the treatment of edema in patients with Bright's disease unless all other measures have failed*. The effectiveness of mercurial diuretics in the nephrotic syndrome is much less than in cardiac edema.

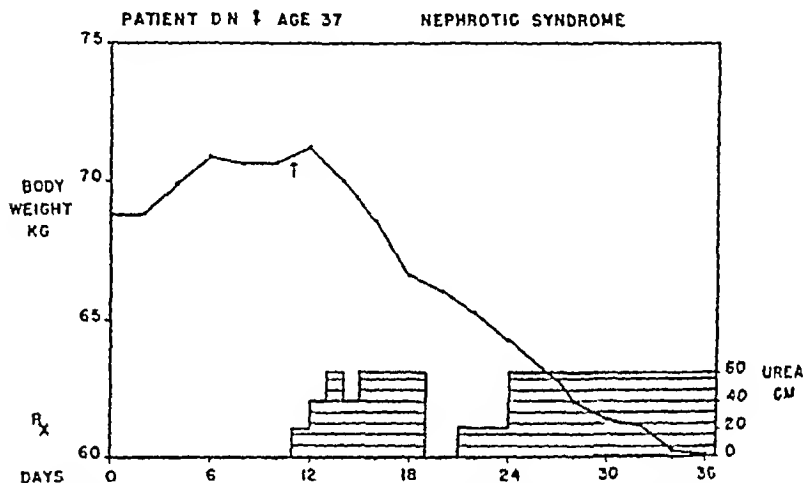


Fig 177—Patient D N a woman aged thirty-seven, was admitted with anasarca, hypoproteinemia and marked proteinuria with only a few formed elements in the sediment. Hypertension was not present. Four years previously this patient had had a similar episode with complete spontaneous remission. With continued rest in bed and a low sodium diet, edema remained unchanged during this admission. Urea therapy was begun with fluids restricted to 1500 cc daily, and a prompt diuresis followed. The time relationship between the administration of the urea (ten days) and the maximum diuresis strongly suggests that the urea was an effective agent in inducing the diuresis.

Urea—Urea is a well known but infrequently used diuretic agent. Its effectiveness depends upon the withdrawal of water and sodium from the body in the elimination of the administered urea. To be effective, then, it is obvious that patients *should not be allowed to increase their fluid intake when urea is being given*. One of the errors in using urea as a diuretic is the failure to direct attention to this point. The unpalatability of urea may be overcome to some extent by adding it to fruit juice and by administering graded doses such as 5 gm three times daily, slowly increasing the individual dose until a total dose of 15 to 30 gm daily has been attained. Urea should not be

employed as a diuretic agent in patients with an appreciable increase in fasting blood urea nitrogen or nonprotein nitrogen. Conversely, it is unusual to obtain much of a diuretic effect with urea until its administration has induced a rise in blood urea level. It is well to follow the blood urea or the nonprotein nitrogen level of the blood at frequent intervals during the course of this therapy. When urea administration interferes with adequate caloric intake, its usefulness is lost.

Patients vary greatly in their response to urea. Occasionally one encounters striking improvement (Fig 177). There is no evidence to indicate that the administration of urea aggravates the underlying renal disease. It is to be appreciated, however, that the excretion of 45 to 90 gm of urea daily increases the work of the kidney. In contrast to the symptoms which spontaneously accompany azotemia, a rise in blood urea nitrogen as a consequence of urea administration is not associated with symptoms.

Protein Content of the Diet.—The protein content of the diet of nephritic patients has been the subject of wide discussion and disagreement in recent years. Patients with Bright's disease may exhibit the following disturbances in protein metabolism: (a) proteinuria, (b) hypoalbuminemia, (c) depletion of tissue protein stores and (d) hyperglobulinemia. It is generally agreed, however, that in acute nephritis and in the terminal stages of chronic glomerulonephritis a high caloric intake (carbohydrate and fat) with a restricted protein intake is the diet of choice. The inability of most patients to ingest adequate calories is a greater difficulty than diet selection. Great ingenuity may be required to make the food attractive. Frequent small feedings are tolerated best.

In contrast, much of the disability accompanying the nephrotic syndrome may be attributable to the coexistent disturbance in protein metabolism, particularly the depletion of tissue protein stores and hypoalbuminemia. By the use of diets high in protein it is thought that the body stores of protein and the serum albumin level may be improved. It is not difficult to induce nitrogen retention by increasing the protein intake in patients with the nephrotic syndrome, whereas it is extremely difficult to induce a significant increase in serum albumin level. When a diet of high protein content is ingested, one observes an increase in the excretion of protein as well as nonprotein nitrogenous substances. Thus such a diet acts to some extent in a manner similar to an equivalent quantity of urea. Fixed acids derived from protein in the diet may also decrease edema by increasing excretion of fixed base.

Not all patients with the nephrotic syndrome can tolerate comfortably a diet of high protein content, and since there is considerable debate as to the advisability of such a diet, it is well to point out that a positive nitrogen balance may also be obtained with a diet of only

moderate protein content but of high caloric content. In normal subjects it has been demonstrated that nitrogen balance may be maintained with a diet as low as 30 gm of protein per day when total calories are adequate. Whether vegetable protein is superior to animal protein in the treatment of patients with renal disease remains to be proved.

In the authors' experience, the administration of a diet of high protein content to a patient with the nephrotic syndrome, massive proteinuria and a recent history of poor intake of food, has been followed by considerable improvement in well-being, although the accumulation of edema fluid remained essentially unchanged.

Amino Acids.^{*}—Amino acid therapy has been advocated as a method of inducing a positive nitrogen balance and as a means of improving the serum albumin level of patients with the nephrotic syndrome. Supplementary amino acid administration would, in general, be similar in effect to increasing the protein intake of the diet.

TABLE 1
SUPPLEMENTARY AMINO ACID THERAPY AS A DIURETIC AGENT

Patient	Type of Therapy*	Result
R S	60 gm /day p o 8 days	Moderate diuresis with loss of weight at increasing rate
J G	70 gm /day p o 10 days	Rising curve of weight due to progressive nephrotic edema was unchanged
W H	60 gm /day p o 30 days	Edema increased in spite of therapy

* Sodium and fluid intake maintained at a constant rate.

It is evident, however, that with supplementary amino acid therapy one is certain of providing all of the essential protein constituents, and in the case of impaired digestion it is possible that amino acids administered as such orally might be absorbed somewhat better in certain edematous patients than equivalent quantities of dietary protein. Amino acids may be administered intravenously to patients whose intake of protein is necessarily restricted because of anorexia, nausea and vomiting.

Thus far most preparations of amino acids have two disadvantages (a) unpalatability and (b) relatively high sodium content. Both of these disadvantages are being corrected, however, and in the near future there should be available palatable amino acids with a low

* The authors are indebted to Dr. Earl L. Burbidge of Frederick Stearns & Company for the supply of amino acids.

sodium content Some of the poor clinical results encountered in the past have been due, no doubt, to the large quantity of sodium which the amino acid preparations contained (Table 1)

Intravenous administration of amino acids is complicated by the local irritation to the veins which may result in thrombosis and thrombophlebitis and by untoward symptoms which occur when the amino acid solution is given too rapidly In most instances, little is gained by administration of amino acid solutions intravenously to patients who can ingest moderate quantities of protein

The effectiveness of amino acid therapy in restoring protein reserves and serum albumin presupposes no impairment to the synthesis of protein in patients with the nephrotic syndrome Aside from their usefulness in improving nitrogen balance, amino acids serve as a source of urea and hence may act as a diuretic agent on this basis That a diuresis does not occur uniformly in patients maintained on an adequate protein intake and given supplementary amino acid therapy is indicated in Table 1

Therapy Designed to Increase Plasma Colloid Osmotic Pressure Directly.—Many attempts have been made in recent years to improve the plasma oncotic pressure of patients with the nephrotic syndrome by administering colloid solutions intravenously No attempt will be made to review all of these studies, but the authors wish to report their own experiences with the use of concentrated human serum albumin, globin and gelatin

The theoretical advantages of attempting to remove edema fluid by increasing plasma colloid osmotic pressure are obvious The problem lies in obtaining a safe, effective and inexpensive substance which may be administered over long periods of time without cumulative toxicity The most readily available solution is citrated plasma This is effective in increasing the plasma colloid osmotic pressure and is a safe agent, as far as immediate administration is concerned, except in patients with congestive heart failure There are, however, two serious problems associated with its use Plasma, either dry or liquid, contains not only its normal content of sodium chloride but also a large amount of sodium citrate The total sodium equivalent, therefore, in 70 gm of plasma protein may amount to 117 gm expressed as sodium chloride This is undesirable in the management of a patient who presents as one of his primary problems an inability to excrete sodium It is probable that the lack of success with plasma (except specially prepared dialyzed plasma) in the treatment of nephrotic edema is due to its high sodium content Recently a new complication has appeared with the clinical administration of plasma, i e., the possibility of inducing homologous serum jaundice The increasing frequency of this complication and the danger to patients with nephritis further limit the use of plasma If plasma is employed, it should be obtained

from one or two compatible donors rather than from a relatively large pool

Whole blood exerts an effect comparable to plasma with the exception that even larger quantities of protein are provided for metabolic uses. Since whole blood may be derived from one donor in comparison to pooled plasma, the probabilities of transmitting the agent of

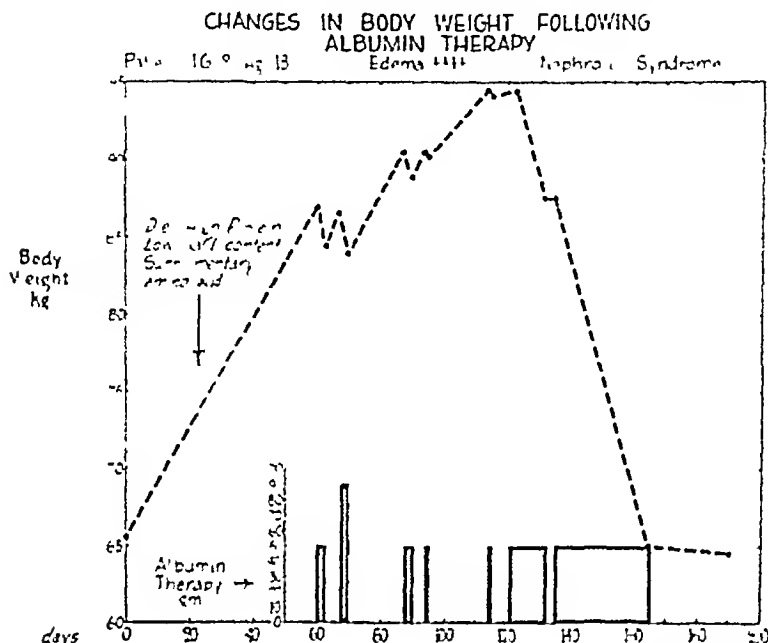


Fig 178—Patient J G, a woman aged eighteen (see Figs 175 and 180), had severe nephrotic syndrome at this time with minimal nitrogen retention and intermittent slight hypertension. Low salt human albumin produced an effective diuresis on all occasions that it was administered. She was maintained on a constant high protein diet and fluid intake throughout the control and treatment period (From Thorn G W, Armstrong, S H, Jr Davenport V D, Woodruff, L M and Tyler, F H. Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation XXX The Use of Salt-Poor Concentrated Human Serum Albumin Solution in the Treatment of Chronic Bright's Disease J Clin Investigation, 24 S02, 1945)

homologous serum jaundice are less. Furthermore, since many patients with renal failure are anemic, the administration of whole blood may be indicated in the treatment of the anemia.

The possibility of hemolytic transfusion reactions is a major contraindication to repeated transfusions in patients with Bright's disease. Although most of these reactions may be obviated by extreme care in matching of the blood, including Rh typing and careful crossmatching,

obscure hemolytic reactions do occur in patients given multiple transfusions

Concentrated Human Serum Albumin.—Human serum albumin as prepared by the technic of Cohn and his coworkers has many theoretical and practical advantages over other colloid solutions. Its effect on the edema of Bright's disease, particularly that due to the nephrotic syndrome, has been studied in some detail^{7, 8, 9}. The effectiveness of intravenous administration of concentrated human albumin of low salt content is demonstrated in Figure 178. The preparation used in these experiments contained only 1.6 gm of salt per volume of solution sufficient to hold 1 liter of plasma water at normal colloid osmotic

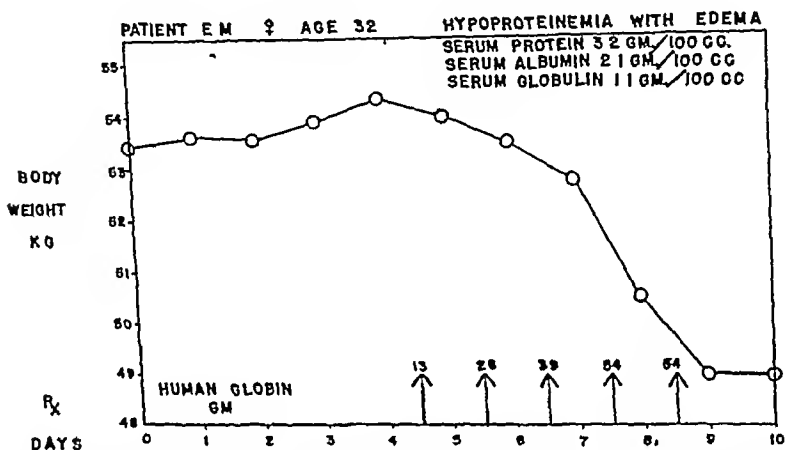


Fig 179—Patient E. M., a woman aged thirty-two, with moderate edema and hypoproteinemia but without other manifestations of the nephrotic syndrome, showed a good diuretic effect from purified human globulin on this occasion. There were no febrile or other reactions to therapy.

pressure. This is a remarkable difference when compared to the 11.7 gm present in an equivalent quantity of citrated plasma. Fortunately, most of the substances in blood and plasma (including the agent of homologous serum jaundice) which tend to produce reactions are also removed by fractionation. In several thousand administrations of human serum albumin no cases of jaundice have been observed.

In patients with the nephrotic syndrome in whom edema is associated with a low colloid osmotic pressure due to reduced serum albumin, it would appear that concentrated human albumin is a nearly ideal diuretic agent. The limiting factor at present is its expense. During the war large quantities of human albumin were prepared from blood donated by the public through the Red Cross. At present it is available commercially but only at a very high cost. Unfortu-

nately, patients with the nephrotic syndrome and proteinuria tend to excrete a large percentage of albumin which is administered intravenously, and hence rather large and continued dosage is necessary. In general it is desirable to give 50 gm of human albumin per day, administered slowly by intravenous drip. No difficulties have been encountered when the solution was given at a rate of 10 gm of albumin per hour. Albumin represents the ideal naturally occurring colloid and is safe except in rarely encountered situations where the ability of the vascular system to compensate for the greatly increased circulating volume is exceeded.

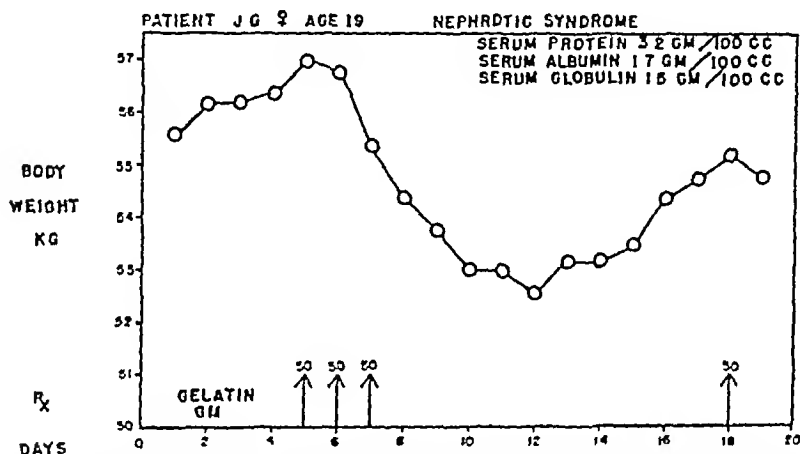


Fig 180—Patient J G, a woman aged nineteen, had severe nephrotic edema and made an unusually good response to gelatin. A subsequent attempt to produce prolonged diuresis in the same patient with gelatin led to nausea and vomiting and only a slight diuretic effect of gelatin.

Globin.^o—Because of the expense of preparing salt-poor human albumin, it seemed desirable to investigate other fractionation products of whole blood. With this in mind, we have tested preparations of human globin obtained from the hemoglobin which is ordinarily discarded in the preparation of plasma or albumin. Purification of this product permits one to administer 25 to 50 gm daily without untoward reaction. That this colloid solution is capable of inducing a diuresis in a patient with the nephrotic syndrome is illustrated in Figure 179. Its effectiveness has not been uniform, however, and final evaluation of its indications and dangers has not been made.

* The authors are indebted to Dr. Max M. Strumia, Bryn Mawr Hospital, Bryn Mawr, Pennsylvania, and to the Smith Kline & French Laboratories for the globin used in these studies.

Gelatin.^{*}—Purified preparations of gelatin are also now available and appear to be fairly well tolerated by most patients. They represent an inexpensive as well as an effective means of raising the colloid osmotic pressure of the plasma. Preparations vary considerably in their average molecular weight. The effect of a short term of treatment with one of these preparations is shown in Figure 180. Some indication of toxic reaction has been observed with long-continued administration of gelatin, and care must be taken not to overload the vascular system. It should be noted that the clinical response objectively and subjectively to 50 gm of *albumin* injected intravenously day after

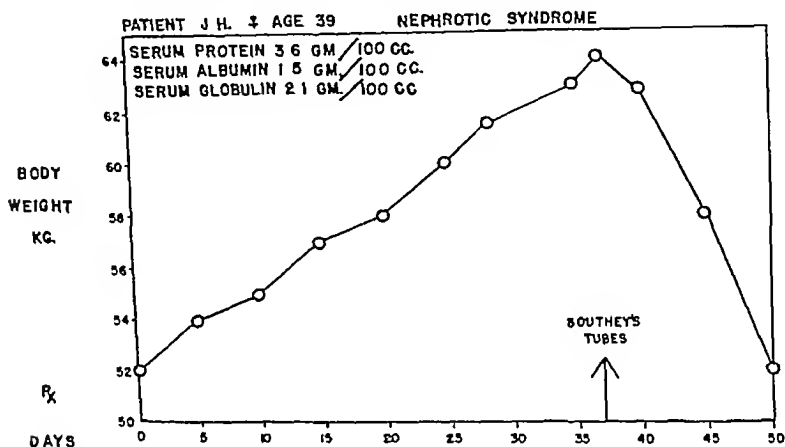


Fig 181—Patient J H, a woman aged thirty-nine with the nephrotic syndrome, failed to respond to any available diuretic measure. When the situation became quite serious, Southey's tubes were inserted with the prophylactic administration of penicillin. A striking loss of edema fluid was followed by great clinical improvement.

day is much better and more consistent than that following the injection of the preparations of globin and gelatin which we have had available.

Acacia and Isinglass.—Acacia and more recently isinglass have also been administered intravenously as an effective means of increasing the plasma osmotic pressure in the treatment of nephrotic edema. Unfortunately, acacia is deposited predominantly in the liver and appears to depress the synthesis of the serum albumin.¹⁰ The effectiveness and dangers of isinglass have not been studied sufficiently, and therefore its use cannot be recommended at this time.

Southey's Tubes—Certain patients with massive edema of the extremities may derive marked benefit from the use of Southey's tubes.

^{*} The authors are indebted to Dr William F Wenner of The Upjohn Company for the gelatin used in these studies.

when other measures fail or are unavailable. With the use of penicillin and other antibiotic agents it is relatively safe to employ this direct method of reducing localized accumulations of fluid. An instance of striking improvement following the implantation of Sonthey's tubes is illustrated in Figure 181.

Intercurrent Infections.—The striking diuresis which occasionally occurs in patients with the nephrotic syndrome during an intercurrent infection or febrile episode is well known. Recently, Janeway¹¹ has reported on the beneficial effect of measles as a therapeutic measure in inducing a diuresis in children with lipid nephrosis. Since most adults are immune to the benign childhood virus infections, this approach is not as likely to be successful in older patients as in children and infants.

SUMMARY

In patients with Bright's disease, edema may constitute a serious and disabling complication. In the absence of specific therapy for the underlying renal disease, it may become necessary and desirable to promote a diuresis. Of the measures which are available it appears that sodium restriction and digitalization in patients with acute nephritis and cardiac failure may prove lifesaving.

Patients with the nephrotic syndrome must also be maintained on a low sodium intake, an acid ash diet and supplementary urea by mouth. In addition, colloid solutions of low sodium content administered intravenously may also prove beneficial. Of these, human serum albumin appears to be the most desirable and effective. There is no evidence that the promotion of a diuresis with consequent clinical improvement affects appreciably the natural course of chronic Bright's disease.

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even though malignant it may persist for years without causing symptoms

TREATMENT—Biopsy should be made if the tumor cannot be completely excised in order that its nature may be determined. Most of these growths are radioresistant but occasionally one is found to be radiosensitive.

Neurofibromatosis.—Within this group occur the peculiar constitutional neoplastic processes of von Recklinghausen's disease. The individual with this condition almost invariably has numerous *café-au-lait* spots on the skin and sometimes nevi and hemangiomas. In addition, mental, psychic and skeletal changes may be present. Osseous defects cause deformities of the skull and vertebrae. The tumors associated with this lesion are neurofibromas of various types, their sites may be cutaneous, subcutaneous or visceral. There is a very marked familial tendency in this disease.

TREATMENT—Decisions as to therapeutic procedure must be made on the findings in the given case. It is believed that the tumors associated with this disease will become malignant from 10 to 15 per cent of the cases. The neurofibromas are frequently multiple and may occur in areas difficult to approach surgically. One of our cases had a plexiform neuroma about 10 to 12 cm. in length located in the posterior mediastinum (Fig. 67).

DISCUSSION AND SUMMARY

The recognition of causes in any problem is the basis for its solution. Inasmuch as we are attempting to control a disease of which so little is known, especially as regards etiology, it is apparent that we are faced, at the very beginning of our efforts toward control, with a formidable task. However, it is unnecessary that a disease be completely understood before measures for its control may be undertaken. There is still much to learn about diseases such as tuberculosis, syphilis, diarrhea of the newborn, and many other conditions known to be reasonably amenable to control and significant advances have been made in reducing the mortality from them.

The chief difficulty in our problem of control of cancer in children arises from the very nature of the neoplastic disease itself. There is hardly any effort on the part of the body in this disease to utilize defensive measures such as occurs in almost all other pathologic conditions. To control a neoplastic disease the tumor must, therefore, be removed from the body or rendered inactive. Such measures require prompt diagnosis so as to permit these procedures to be utilized at a period early enough in the tumor's existence, as well as in the patient's, to bring about a favorable result.

It is recognized of course, that some types of tumors in childhood, especially some of those of the lymphatic and nervous systems, are

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THE USE OF STREPTOMYCIN IN THE TREATMENT OF MENINGITIS

TOM FITE PAINE, M D ° AND MAXWELL FINLAND, M D , F A C P †

AMONG the bacterial meningitides, those least favorably affected by the sulfonamides and penicillin are the ones which are caused by gram-negative bacilli and, of course, the cases of tuberculous meningitis. Streptomycin has proved to be the most effective agent now available in the treatment of these infections.^{1 2} Streptomycin alone also appears to be at least as effective, or even more so, than the combination of sulfonamides and rabbit type specific antiserum in the treatment of *Hemophilus influenzae* Type b meningitis.^{3 4} An acquaintance with the proper use and limitations of streptomycin in this very serious group of infections is, therefore, essential for those who may be called upon to treat such cases.

INCIDENCE OF CASES OF MENINGITIS POTENTIALLY SUITABLE FOR STREPTOMYCIN THERAPY

In a series of 3178 cases of bacterial meningitis reported by Neal,⁵ the over-all incidence of cases due to gram-negative bacilli was about 5 per cent. In infants and young children, the incidence of gram-negative bacillus meningitis was higher than in adults. In patients below the age of 3 years, 9.5 per cent of 1077 cases were due to gram-negative bacilli⁶ and in a series of 149 fatal cases of bacterial meningitis in patients below 3 years of age, 32 per cent were due to such organisms.⁶

Most of the gram-negative bacillus infections of the meninges in infants and children are caused by *Hemophilus influenzae*. The coliform organisms rank next but are much less frequent. In Neal's series,⁵ 8.5 per cent of the cases in patients under 3 years of age were due to *Hemophilus influenzae* and 0.56 per cent to *Bacillus coli*.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

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Among the 149 fatal cases of bacterial meningitis in patients below 3 years of age *Hemophilus influenzae* accounted for 26 per cent and the colon bacillus for 6 per cent⁶ Other gram-negative bacilli which have been encountered less often are *Klebsiella pneumoniae* (Friedlander's bacillus),^{5,7} the typhoid-dysentery group,⁸ *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*),⁹ the proteus group,¹⁰ *Aerobacter aerogenes*,¹¹ *Pasteurella tularensis*¹² and others

Tuberculosis of the central nervous system is a common condition, comprising 31 per cent of Neal's series of 3178 cases⁵ Here, again, the highest incidence of the disease is among children

It is to be borne in mind that streptomycin also exerts antibiotic action against gram-positive and gram-negative cocci, though these organisms are generally considered to be affected best by penicillin and sulfonamides In occasional infections due to such organisms, streptomycin has proved useful when the other agents apparently failed¹³⁻¹⁴ It may, therefore, be considered as a substitute for, or as an adjunct to therapy with other antibacterial agents under such conditions

HEMOPHILUS INFLUENZAE MENINGITIS

This is primarily a disease of infancy and early childhood, most of the cases are caused by the smooth Type b strain The usual history in such cases is that of a mild upper respiratory infection followed by signs of meningitis The organisms probably reach the meninges by the blood stream after invasion through the respiratory tract.

The over-all mortality in this disease has been reduced by combined sulfonamide and type-specific rabbit antiserum therapy from nearly 100 per cent to between 15 and 50 per cent¹⁵⁻²⁰ Streptomycin now provides the best available means for treating this disease. Furthermore, since the action of streptomycin is not type-specific, it may be used in *Hemophilus influenzae* infections due to strains other than those of Type b

The mortality rate in the 100 cases of *Hemophilus influenzae* meningitis treated with streptomycin under the auspices of the National Research Council¹ was 17 per cent. Streptomycin was given to many of these patients, however, only after other forms of therapy had proved unsuccessful. In the treatment of twenty-five cases with streptomycin alone or combined with other therapeutic agents, Alexander⁴ reported three deaths Strains of *Hemophilus influenzae* resistant to streptomycin developed in two of her cases There were two deaths in the nine cases treated by Weinstein,³ one of these deaths was due to a secondary staphylococcal infection

The experience at the Boston City Hospital in the treatment of *Hemophilus influenzae* meningitis has been equally encouraging In fifteen cases treated to date there has been only one death, ten of these fifteen patients were under 1 year old.

Treatment of Hemophilus Influenzae Meningitis—Streptomycin

—The administration of streptomycin by the intramuscular or intravenous route alone cannot be depended upon to maintain adequate concentrations of the drug in the cerebrospinal fluid^{1, 21-27} Little if any streptomycin is detectable in the cerebrospinal fluid after injection by these routes when there is no meningitis, and only relatively low concentrations are found in the cerebrospinal fluid under these conditions in cases of meningitis. Consequently, it is advisable to give the antibiotic by both the parenteral and intrathecal routes in the treatment of meningitis. In infants and young children the administration of 0.5 to 2 gm intramuscularly and 50 mg intrathecally during each twenty-four hour period usually results in the maintenance of high concentrations in the blood and cerebrospinal fluid. Levels of 3 to 6 units per cubic centimeter of streptomycin may still be found in the cerebrospinal fluid twenty-four hours after the intrathecal injections. Most of the pathogenic strains of *Hemophilus influenzae* that have been tested are inhibited by 1 to 5 units per cubic centimeter.²

Administration of Streptomycin—Streptomycin is supplied commercially as a dry sterile powder, either as the hydrochloride or sulfate. Each vial contains the equivalent of 0.5 gm or 1 gm of pure streptomycin base, each gram being equivalent to 1,000,000 units. Sterile isotonic saline is added to the vial to make up the desired concentration. Solutions are less stable than the dry powder and should be kept in a refrigerator.

Intramuscular Injection—The administration of 30 to 75 mg per pound of body weight or a total of 0.25 to 2 gm daily to infants and young children in divided intramuscular doses at six hour intervals is recommended. In adults 1 gm every four or six hours is suggested. The gluteal muscles, the lateral aspects of the thigh and the triceps may be used in rotation. Each gram of streptomycin may be dissolved in as little as 4 to 5 cc of sterile, pyrogen-free distilled water or isotonic saline, making possible the administration of a large amount of streptomycin in a relatively small volume. Procaine hydrochloride, 1 cc of a 1 per cent solution, may be added to 4 or 5 cc of the streptomycin solution if desired, but the discomfort of intramuscular injection is probably minimized best by keeping the volume of injected material as small as possible. Intravenous administration is rarely indicated as the drug is absorbed very rapidly from intramuscular injections with peak levels in the blood usually being reached within thirty minutes. Intravenous injections are more often followed by immediate untoward reactions. Subcutaneous injections may be given but they produce pain and irritation more frequently. Intramuscular therapy should be continued for four or five days after the clinical and laboratory findings have indicated that the infection has subsided.

Intrathecal Injections—Streptomycin may be applied safely in ther-

apeutic doses to the central nervous system. The daily administration of 50 mg (50,000 units) to infants and 50 to 100 mg. to adults is recommended. In newborn infants it may be advisable to use 25 mg for the initial intrathecal doses. It has been found useful to add 20 cc of sterile isotonic saline solution to a vial containing 1 gm of streptomycin, making a final dilution of 50 mg per cubic centimeter, and then to use this vial exclusively for intrathecal injections throughout the illness. At the time of the injection, 1 cc of the streptomycin solution is withdrawn from the vial mixed with another 3 to 5 cc. of sterile isotonic saline. The solution is injected slowly into the lumbar subarachnoid space after the slow withdrawal of a larger volume of cerebrospinal fluid. Streptomycin may also be injected into the lateral cerebral ventricles through the anterior fontanelle in infants or into the basal cistern when a block is suspected. In severely ill patients the first two or three intrathecal doses may be administered at twelve-hour intervals and subsequent ones every twenty-four hours. Intrathecal injections should be continued until the patient has shown marked clinical improvement and the cultures and other cerebrospinal fluid findings indicate that the infection has been controlled.

Continued administration of streptomycin intrathecally after the temperature has reached normal may be associated with a secondary febrile response and was noted in about half of the patients treated in this hospital. In most cases the temperature reached normal between the fourth and seventh day of streptomycin therapy and the secondary rise in temperature occurred quite promptly thereafter. In some cases there is also an increase in the number of leukocytes, largely polymorphonuclear, in the cerebrospinal fluid associated with this secondary fever. This fever usually subsides and the number of polymorphonuclear cells in the cerebrospinal fluid drops promptly after the intrathecal injections are discontinued.

Sulfadiazine—Sulfadiazine is not indicated initially in most cases of *Hemophilus influenzae* meningitis since streptomycin alone in adequate doses will probably control the infection. However, in very young infants, in patients who are extremely ill or where treatment is begun late in the course of the disease, sulfadiazine should be given, preferably by hypodermoclysis. The sulfonamide is also indicated if the patient fails to respond to streptomycin or when there is evidence of a relapse of the infection during the streptomycin treatment.

Four cases have been reported in which resistant strains of *Hemophilus influenzae* appeared during streptomycin therapy.^{4, 28, 29} The institution of sulfadiazine therapy in such cases is obviously indicated and there is probably no advantage in continuing streptomycin when that occurs. The appearance of secondary infections in the ears, nasopharynx, meninges or elsewhere while the patient is receiving strep-

streptomycin treatment is also indication for sulfadiazine or penicillin, depending on the type of secondary infecting organism³

Penicillin—There is little evidence that penicillin, as ordinarily used, is of therapeutic value in the treatment of *Hemophilus influenzae* meningitis although occasional cases have been reported in which the organism proved to be sensitive to penicillin and a good response followed treatment with this antibiotic and sulfonamides³⁰⁻³² Penicillin is certainly indicated in the treatment of complicating secondary infections with susceptible organisms during or after streptomycin therapy

Antiserum—The use of specific *Hemophilus influenzae* Type b rabbit antiserum is not recommended for the routine initial therapy of most cases of *Hemophilus influenzae* meningitis As already stated, it may be given to very young infants, to those who are extremely ill or if treatment is begun late in the disease It is indicated if the patient fails to respond or if there is evidence of a relapse of the influenzal infection during streptomycin treatment Tests for sensitivity to rabbit serum should be done and the antiserum should be given essentially according to the recommendations of Alexander¹⁶ A dose of specific antiserum equivalent to 100 mg of antibody nitrogen is given in saline solution by intravenous infusion over a period of two hours The volume of fluid suggested is 10 cc per kilogram of body weight and this may be added to the infusion containing sodium sulfadiazine solution Additional antibody, 25 mg per day, may be given intramuscularly if the progress is not satisfactory or if the serum of the patient, diluted 1:10, fails to produce capsular swelling with the infecting strain

Examination of Cerebrospinal Fluid.—The progress of the disease and the effect of therapy on the course of the infection can be intelligently followed only with the aid of frequent examinations of the cerebrospinal fluid This should be done daily until the infection is controlled and at longer intervals thereafter until the fluid returns essentially to normal

Examination of the cerebrospinal fluid should include

1 **Stained smears** The presence of gram-negative bacilli in the stained smears is sufficient indication for the institution of streptomycin therapy Gram-stained smears of the cerebrospinal fluid during therapy are of help in determining the presence or absence of *Hemophilus influenzae* or other secondary invaders

2 **Culture** A culture should be made of the cerebrospinal fluid obtained at the time of the first lumbar puncture which should be done before any antibacterial therapy is given One should not wait for the result of this culture before starting streptomycin therapy, but the antibiotic should be given if gram-negative bacilli are found in the stained smear Cultures should be made of all specimens of

cerebrospinal fluid obtained during therapy in order to demonstrate the persistence or recurrence of *Hemophilus influenzae* or the appearance of secondary invaders

3 *Cell count* A total leukocyte count should be performed on each specimen of cerebrospinal fluid and a differential cell count included. (The chamber differential count is adequate) This provides a simple indication of the progress of the disease and may even be used as a guide for therapy. If the infection is subsiding, the total cell count diminishes and the percentage of mononuclear cells increases.

4. *Sugar and protein.* Determinations of the sugar and protein content of the cerebrospinal fluid are also helpful in following the course of the infection. The sugar rapidly increases to a normal level when the infection is subsiding or decreases in the presence of a relapse or complicating secondary infection of the meninges. The protein content decreases to a normal level somewhat less rapidly than the return of the sugar to normal when the infection is under control. Correspondingly, a relapse or secondary meningeal infection would be attended by an increase in protein content. In interpreting the sugar content the effect of recent infusions of glucose must be considered.

Response to Streptomycin Therapy.—Cultures of the cerebrospinal fluid in all of the cases of *Hemophilus influenzae* meningitis treated at this hospital have been negative following the first intrathecal injection of streptomycin. This was associated with an increase in the sugar and a decrease in the protein content of the fluid. There was a rapid decrease in the total number of leukocytes in the cerebrospinal fluid, with a change from a polymorphonuclear to a mononuclear predominance.

The clinical response usually lags slightly behind the laboratory evidence of subsidence of the meningitis. Clinical improvement is usually striking during the first two to four days. During this time there is a return to a normal state of consciousness, subsidence of convulsions or irritability, and the infants begin to feed well. The temperature gradually falls to normal over a period of four to seven days.

A typical response to streptomycin treatment in a case of *Hemophilus influenzae* meningitis is shown in Figure 182.

Neurologic Sequelae.—Evidence of neurologic damage has been uncommon in patients with influenzal meningitis who recovered following streptomycin therapy. In the group of fifteen patients treated at this hospital, only one showed evidence of permanent neurologic damage. Treatment in this infant was begun on about the sixth day of the disease and following recovery the infant was apparently deaf and blind.

Interpretation of Persistent or Recurrent Fever.—The occurrence of a secondary rise in temperature or the persistence of fever during or after apparent recovery from *Hemophilus influenzae* meningitis on streptomycin therapy is particularly disturbing to the physician. Some of the principal causes for this fever may be considered briefly.

1 *Relapse of the Original Infection*—This eventuality was not uncommon in the days of combined sulfonamide-antiserum treatment of influenzal meningitis. It is much less frequent in patients adequately

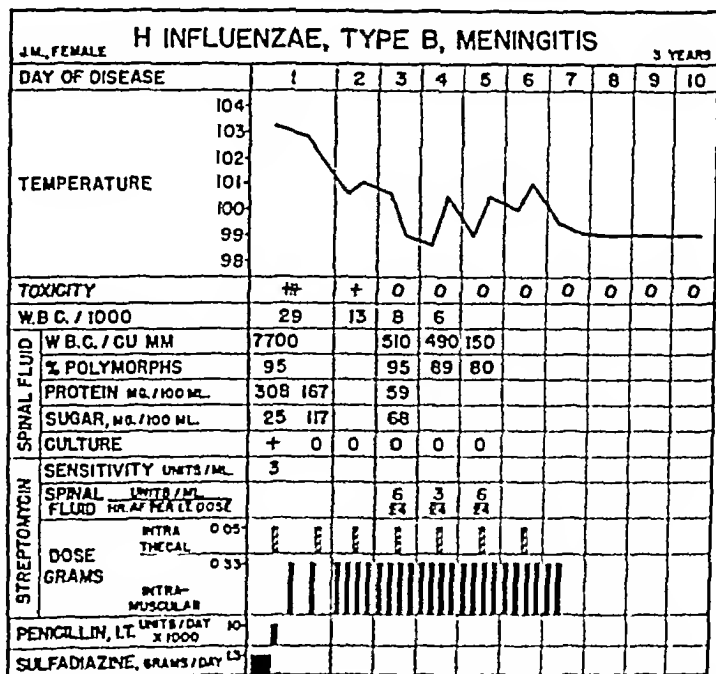


Fig 182—Therapy, clinical response and relevant findings in the cerebrospinal fluid in a case of *Hemophilus influenzae* Type b meningitis in which treatment with streptomycin was begun early in the disease. The secondary rise in fever is probably attributable to streptomycin.

treated with intrathecal and intramuscular streptomycin. Such a relapse is heralded by an exacerbation of the clinical evidence of meningitis and the reappearance of organisms in smears and cultures of the cerebrospinal fluid. There is also an increase in the number of cells, the percentage of polymorphonuclear forms and the protein content, with a decrease in the level of sugar in the fluid. The strain of organisms that reappears during streptomycin therapy is likely to be extremely resistant to the action of streptomycin. Specific antiserum and sulfadiazine are then indicated. It is emphasized, however,

that in cases which are adequately treated with streptomycin by both the intrathecal and parenteral routes this phenomenon is rare

2 *Secondary Infection*—Complicating infections by organisms relatively insensitive to streptomycin may occur in the ears, nasopharynx, the meninges or elsewhere during or after streptomycin treatment of influenzal meningitis. The physician must watch for such a development and institute additional therapy in the form of sulfadiazine or penicillin, or both, as indicated

3 *Streptomycin Fever*—As already noted, the appearance of a secondary febrile episode in patients recovering from influenzal meningitis and apparently related to the streptomycin is not uncommon. The course in these patients is characterized by clinical and laboratory evidence of improvement, a gradual drop in the temperature to normal followed by a fairly abrupt exacerbation of fever. This fever usually subsides promptly when the intrathecal injections of streptomycin are stopped. In some patients a slight increase in cells in the cerebrospinal fluid, particularly polymorphonuclear leukocytes, is noted coincident with the fever, and this, too, subsides when the intrathecal injections are stopped. Clinically the patients continue to appear well during this febrile episode. The fever may also be related to the intramuscular injections of the streptomycin and, in that event, it subsides when these injections are discontinued. In order to minimize the occurrence of drug fever, it is recommended that the intrathecal injections be stopped one or two days after the temperature first reaches normal, provided, of course, that other examinations indicate that the infection is completely controlled and that the parenteral therapy is carried out for two or three days longer.

4 *Sulfadiazine Fever*—Drug fever associated with the administration of sulfadiazine is a relatively frequent occurrence in patients receiving this drug for more than one week. It may be associated with a rash. Stopping the sulfadiazine results in rapid subsidence of the fever, if the two are related, and the rash, if present, also clears rapidly.

5 *Serum Sickness*—The incidence of serum sickness following administration of antiserum varies considerably. It usually appears seven to fourteen days after administration of the serum and is often associated with fever, urticaria, arthralgia and lymphadenopathy.

MENINGITIS DUE TO OTHER GRAM-NEGATIVE BACILLI

Meningitis due to gram-negative bacilli other than *Hemophilus influenzae* may occur in any age group. No one of these organisms predominates in such cases in adults, but colon bacillus infections are more common in infancy. Most of the cases follow direct implantation of the organisms into the meninges by trauma or by contaminated lumbar puncture or they occur by extension from an adjacent focus.

of infection in the nasal sinuses, ears, mastoid or meningocele. Occasionally they occur in association with septicemia resulting from distant foci of infection in the gastrointestinal or genitourinary tract or elsewhere. Mortality rates in this type of infection depend upon many factors but they are generally quite high (from 50 to 100 per cent). The sulfonamides have been helpful but their use has not reduced the mortality to any marked extent.^{9, 12, 33-37}

Cases of meningitis due to a wide variety of gram-negative bacilli have been treated with streptomycin by many workers^{1, 20, 36-42} and the results, though variable, were quite gratifying. The effects observed at this hospital have been encouraging. A group of six such cases have been treated, the causative organism was *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*) in three cases and *Bacillus proteus*, *Aerobacter aerogenes* and *Hemophilus para-influenzae*, each in one case. Five of these patients have recovered. The fatal case was one due to *Pseudomonas aeruginosa* in which the organism became totally resistant to streptomycin after seventeen days of treatment with the antibiotic and remained so. Some of these cases are reported elsewhere.⁴²

Treatment.—*Streptomycin*—Streptomycin should be administered essentially as already described for *Hemophilus influenzae* meningitis and the dosage, both intramuscular and intrathecal, is the same and depends on the age of the patient. Secondary fevers related to the streptomycin have been noted with equal frequency in this type of case. The period of streptomycin therapy depends on the clinical and laboratory evidence of subsidence of the infection. In certain cases of meningitis due to *Pseudomonas aeruginosa*, an organism which is often naturally quite resistant to streptomycin, cerebrospinal fluid cultures may not become negative for several days after the therapy is begun. In one such case⁴² streptomycin therapy was given over a period of one month before organisms disappeared completely.

The possibility of the development of extremely resistant strains of organisms exists during streptomycin therapy, as already noted. This can readily be determined by growing the organism in media containing varying concentrations of streptomycin. If the organism is found to be resistant, further streptomycin therapy will probably be of no avail and its administration may be discontinued.

Penicillin—Most of the gram-negative bacilli encountered in meningitis are quite resistant to penicillin. Indeed many such strains produce a penicillin inhibitor known as penicillinase. There is, therefore, no indication for the use of this agent initially. Should secondary infections due to penicillin-sensitive organisms arise, penicillin would be indicated and should be given in generous doses.

Sulfonamides—Most of the cases of gram-negative bacillus meningitis will probably respond to streptomycin alone. However, if the

usually fatal, but it must be emphasized that, particularly in tumors of the juvenile age group, cures of practically all types of malignant neoplasm are known

Our present major effort at control therefore begins with diagnosis and the diagnosis of any disease can be made only if its possible presence is recognized. Many people are unaware that children may develop cancer. Furthermore it is not generally appreciated that cancer and its allied diseases constitute an important cause of childhood mortality in this country.⁷

The foregoing discussion reviews the major symptoms and signs which the usual childhood neoplasms may produce. There are two common factors in this entire problem which should simplify the diagnostic approach to any neoplasm in the juvenile period, namely, (a) the unusual symptom complex, and (b) the silent swelling.

The Unusual Symptom Complex.—It is appreciated that any illness causes a child to act contrary to his usual self and that certain maladies produce persistent physiological and psychological changes. Neoplasms produce either constant or *periodic* changes which become evident when one contrasts the child with others of his age group or the individual child with his usual behavior or physical stature.

The child who differs from others in size (either greater or smaller), mentality, or social adjustability may have a tumor.

The child who has a part of his body (leg, arm or head) growing at an unusual rate, or who has an asymmetrical growth of certain parts of the body (one breast, one testicle, etc.) may also harbor a tumor.

The Silent Swelling.—The small or large swelling which occurs at any age period and usually does not show any significant growth or produce any subjective symptoms may be cancer. The traumatic swelling which does not regress or, in the case of a bone, undergo repair in the usual period of time likewise might be the site of a cancer.

Therapy.—It is true that the therapeutic methods in use, chiefly surgery and irradiation, are not universally satisfactory. A vast research program is currently in progress to determine the effects of antibiotics and chemotherapeutic agents in neoplastic disease. Whatever further advances are made, it is reasonable to assume that unless cases of childhood cancer are recognized earlier than they are at present the effectiveness of any therapeutic advance will be minimal. It cannot be sufficiently emphasized that clinically recognizable cancer is not early cancer. The young patient who presents himself with a neoplasm has already lost much time and a rapid and aggressive approach to his problem is required.

What Policies Will Assure an Earlier Diagnosis?—The laity must know that cancer is not only a problem of maturity but is a very

organism is fairly resistant to streptomycin, it is probably wise to administer a sulfonamide along with the streptomycin. Again, in the event of secondary complicating infections by sulfonamide-sensitive organisms, a sulfonamide should be given. Sulfadiazine is the drug of choice and should be given in full doses orally whenever possible. If oral therapy is not feasible, the sodium salt may be given in solution. In adults, 3 gm are given in about 250 cc of physiological saline by hypodermoclysis every twelve hours. Corresponding doses are given to infants and children.

Surgery—Chemotherapeutic and antibiotic agents are no substitute when surgery is indicated. If foci of infection are suspected that may require surgical drainage, the surgeon should be consulted and necessary surgery carried out.

For a discussion of the diagnostic features of meningitis and of the focal complications that may be encountered, the reader is referred to the paper by Keefer⁴³

TUBERCULOSIS MENINGITIS

Meningitis due to the tubercle bacillus often occurs in association with a spread of the disease, or primary dissemination, from a focus of infection in the lungs or elsewhere. The original focus, however, is not always demonstrable.

It is usually a disease of insidious onset, being marked by listlessness, lethargy, irritability, fever and headache over a period of weeks. The more dramatic signs of meningeal irritation or increased intracranial pressure come somewhat later and are usually responsible for the admission of the patient to a hospital.

Heretofore it has been a uniformly fatal disease^{44, 45}. In a number of reported cases treated with streptomycin, the disease appears to have been arrested^{41, 46-48}. The follow-up in these cases was relatively short and a final evaluation of the therapy is not yet possible. The incidence of serious and permanent neurologic damage in these survivors was high. Three cases of tuberculous meningitis have been treated at this hospital. In one patient the disease appears to have been arrested after a treatment period of four months and there has been no evidence of relapse during the ensuing three months.

Diagnosis—Examination of the cerebrospinal fluid during the first few days of the disease usually shows an increase in leukocytes, predominately polymorphonuclears. By the time the patient is seen by the physician, however, the cells usually are almost all lymphocytes. This continues throughout the course of the disease except when foreign substances are injected into the thecal space or secondary bacterial infection supervenes. The sugar content of the cerebrospinal fluid may be only slightly decreased initially but drops progressively as the disease advances. The protein is elevated and a pellicle often

forms in the fluid on standing. The chloride content of the cerebrospinal fluid may be decreased.

The diagnosis depends on demonstrating the acid-fast tubercle bacilli by (1) Ziehl-Nielsen (acid-fast) stain of the pellicle or of the centrifuged sediment of the cerebrospinal fluid, or (2) appropriate culture or guinea pig inoculation of the fluid. Cultural methods now allow the demonstration of tubercle bacilli in a matter of several days rather than in the four to six week period required by older methods.

Streptomycin Treatment.—In cases of tuberculous meningitis streptomycin should be administered by both the parenteral and intrathecal routes and should be carried out for a period of at least four months.⁴⁸ Since the outcome of such cases may well depend on the early institution of therapy, it would seem wise to treat suspected cases as soon as possible and to continue the therapy at least until the results of culture or guinea pig inoculation are known. It is particularly important to obtain cerebrospinal fluid for culture or guinea pig inoculation or both *before* streptomycin is begun since these procedures may yield negative results after the treatment is begun and the diagnosis may then remain in doubt. It should be emphasized that therapy should not be withheld pending the results of the pretreatment cultures or of guinea pig inoculations.

TOXIC EFFECTS OF STREPTOMYCIN

Reactions are not unusual following streptomycin therapy and may be manifested locally and constitutionally.

Local Reactions.—*From Intramuscular Injection*—Pain, tenderness and induration are commonly noted at the site of intramuscular injections. This local reaction is minimized by keeping the volume of injected material at a minimum.

From Intrathecal Injections—Fever and pleocytosis in the cerebrospinal fluid may follow such injections. These reactions are related to the amount of streptomycin injected and to the duration of intrathecal therapy. Injection of no more than 50 to 100 mg. of streptomycin per dose and termination of the intrathecal therapy soon after the infection is controlled will minimize these reactions.

Constitutional Reactions—*Histamine-like Effect*—Flushing of the skin, nausea, vomiting, headache, fall in blood pressure or convulsions may follow immediately after the parenteral administration of streptomycin. These reactions are encountered almost exclusively during intravenous injections, particularly when such injections are given too rapidly. Present lots of streptomycin are practically free of the histamine-like material which produces this immediate reaction. Benadryl has been used successfully to avoid the histamine-like reaction.⁴⁹

Sensitization Reactions—Fever and skin rashes of varying types may follow the parenteral use of streptomycin. These usually appear be-

tween the third and tenth day of therapy. Fever, as noted above, may follow either the intramuscular or intrathecal injection of streptomycin but is more frequent following the latter.

Neurologic Disturbance—Disturbance of function of the eighth cranial nerve, particularly the vestibular portion, may appear following parenteral streptomycin therapy.⁶⁰ Such a reaction is apparently not related to the intrathecal injection of the drug. The disturbance is commonly manifested by an ataxia or, rarely, by deafness. This reaction seems much more common in adults than in children. Compensation for the absence of vestibular reflexes by other postural mechanisms usually occurs in a period of weeks resulting in a considerable or total alleviation of the disability.

Effects on Other Organs—Hyaline and granular casts have been noted in the urine of some patients receiving streptomycin but there has been no evidence of lasting renal impairment.

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THE TREATMENT OF DIASTOLIC HYPERTENSION

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In the treatment of any disease it is important first to seek its cause, for one can then plan prophylactic as well as therapeutic measures for its control. This consideration is of utmost importance in the case of diastolic hypertension. Unfortunately there remain many unsolved problems in the etiology of this disease, and wide gaps exist in our knowledge regarding its natural history.

Nevertheless valuable observations, both clinical and experimental, have been made since Bright first associated cardiac hypertrophy with renal disease in 1836,¹ indicating that occasionally hypertension is due to unilateral pyelonephritis, acute or chronic glomerulonephritis, and adrenal and pituitary tumors. When the exact cause cannot be determined we call the disorder essential hypertension.

There is not space to review the extensive experimental work² that has been done to determine the mechanism of essential hypertension. Peet³ has recently discussed this problem and presented evidence that both the autonomic nervous system and the kidneys are involved in its pathogenesis. The important steps in his hypothesis are as follows: An overactive sympathetic nervous system produces vasoconstriction of the renal arterioles which, in turn, leads to renal ischemia. This picture is very similar to that produced by Goldblatt's clamp⁴ around the renal artery. The only difference in essential hypertension is the millions of "neurogenic clamps" constricting the renal arterioles. It is thought that, if this mechanism persists long enough, pathologic changes take place in the arterioles throughout the body, but especially in the kidney, that make possible the existence of a constant state of renal ischemia. As the disease progresses it usually follows one of three patterns:⁵

1. The heart is predominantly affected and the patients suffer from symptoms of myocardial exhaustion. Over 50 per cent of the cases of essential hypertension belong to this group.

2. Somewhat less than 40 per cent of the patients manifest predominant involvement of the central nervous system.

3. Ten per cent develop marked impairment of renal function and die of uremia.

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About 10 per cent of all patients with essential hypertension develop malignant hypertension. In this condition the hypertension is severe and the course of the disease is rapid.

The importance of ruling out tumor, glomerulonephritis and pyelonephritis as possible causes of hypertension cannot be overemphasized. The urine should always be examined and cultured, for occasionally pyelonephritis may be the responsible factor, and a suitable urinary antiseptic should be started immediately if organisms are found. Although cases with hypertension due to this cause are rare, it is important always to be on the look-out for them. The possibility of a pheochromocytoma must not be overlooked. Recently attention has been called to the fact that continuous hypertension may be produced by this tumor as well as the paroxysmal hypertension which was once regarded as characteristic of this condition.⁶ When histamine is administered to these patients there is a much greater increase in the blood pressure than that obtained in essential hypertension.⁷ Characteristic changes in the blood pressure on standing are also present.⁸ In the case of patients with pheochromocytoma, standing leads to a marked decrease in blood pressure, whereas patients with essential hypertension, as a rule, show an increase in blood pressure when standing. The blood potassium is frequently elevated in cases of pheochromocytoma.⁸ Removal of this tumor is usually followed by a marked lowering of the blood pressure and diminution of symptoms, and the response to postural changes returns to normal.

The presence of a pituitary tumor or chronic glomerulonephritis will require special therapy. Pituitary tumors are treated by surgical removal or radiation therapy. Dietary therapy, as described later on, is the most satisfactory means of treating the hypertension associated with glomerulonephritis. Prevention of infections and sore throats, thus avoiding a recurrence of glomerulonephritis, is especially important.

MEDICAL TREATMENT

The success of medical treatment of diastolic hypertension depends upon an accurate appraisal of the type of high blood pressure present. In each patient the relative involvement of the heart, brain and kidney—especially of the heart—must be carefully evaluated. Although certain investigators have suggested that patients with hypertension have a particular type of personality,¹⁰ our experiences with this disease lead us to consider their responses as a normal reflection of disease upon their individual personality. Their reactions are those of the average individual to illness.

Psychotherapy.—In each patient with hypertension there should be specific personal tutoring. He should be enlightened carefully with respect to the nature of the disease. What "blood pressure" is should

be clearly explained, particularly the fact that the level obtained by the physician is at best a very crude approximation of the daily average blood pressure. We have found that it is best as a rule, with infrequent exceptions, to tell the intelligent patient what his blood pressure level is at all times. After adequate explanation he will not worry as he is likely to do if it hangs as a mystery over him. If he understands the problems involved in his care he will be much more apt to cooperate with suggestions that one considers important for him to follow. It would seem unnecessary as a rule to subject these patients to extensive psychoanalysis.

Rest—The realization that overexertion, excessive emotional strain, long hours at work, and loss of sleep aggravate essential hypertension deserves thoughtful consideration by the doctor and patient. Rest in the recumbent position is without doubt one of the most effective ways of treating hypertension. The strain on the circulatory system is lessened, and frequently severe headache and visual disturbances are relieved. It may not be practicable for a patient to rest for long periods in bed. Over weekends, however, available time can be budgeted to make up for some of the strenuous hours encountered during the week.

Sedatives are important to allay excessive nervousness, and to prevent sleepless nights. They should be used intermittently and changed frequently to avoid the development of tolerance. The barbiturates appear to lower blood pressure by augmenting the fall produced by the recumbent position and by reducing the pressor effects of emotional stimuli.

Dietary Treatment.—This form of treatment is especially helpful in the care of patients with diastolic hypertension associated with impairment of renal function, whether this is due to glomerulonephritis or essential hypertension. Recently it has been suggested for patients without renal impairment^{11, 12, 13}. There are two feasible dietary regimens.

1 *The Rice Diet*—This consists of rice, fruit and sugar. No salt is permitted. It contains, in 2000 calories, 5 gm. of fat, 20 gm. of protein derived from rice and fruit, 468 gm. of carbohydrate, and not more than 0.20 gm. of sodium. Patients are usually able to eat 200 to 300 gm. of rice a day which is equivalent to about 1050 calories. Water is limited to 1000 cc. per day but there is much fluid in the fruit. The additional calories are supplied by sugar and fresh or preserved fruits. The palatability of the rice depends a good deal upon how it is cooked and served. The addition of sugar or lemon juice helps to make it taste better. Although the amount of protein is less than the current "standard" nutritional daily requirements, good results have been obtained in some cases, and the patients have been found to be in nitrogen balance.

2 *The Low Sodium Diet*—The low sodium diet of Grollman is more varied and supplies a larger amount of protein. Adequate protein and a sodium intake of under 0.5 gm a day is accomplished by using milk, dialyzed free of sodium. This diet, like that described above, although difficult to follow, can lower the blood pressure and lead to relief of many of the unpleasant symptoms of hypertension. Patients following these diets must be watched carefully to make sure that they do not develop symptoms of sodium deprivation, particularly during hot weather (anorexia, weakness and impaired mental acuity).

Drug Therapy.—*Potassium thiocyanate* is still used by some in the treatment of hypertension, although many regard it as a hazardous

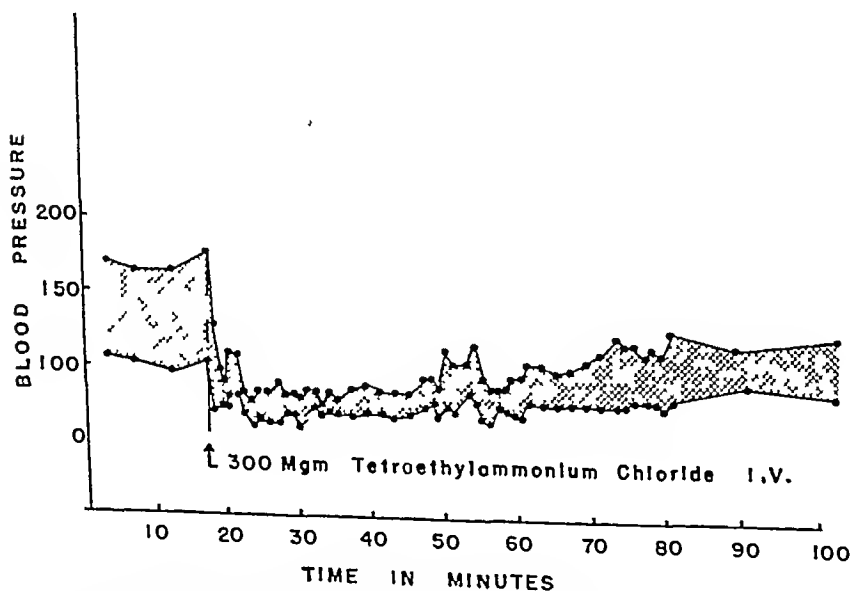


Fig 183—Blood pressure response of J H, aged 58, after the injection of 300 mg of tetrathylammonium chloride intravenously (Courtesy of Dr Fiorindo Simone)

drug.¹⁴ The dosage is best controlled by following the thiocyanate blood level, which should be 8 to 12 mg and should never exceed 15 mg per 100 cc.

Nitrites, both short and long acting, have been used but they are in general unsatisfactory, although longer studies with mannitol hexamtrate may be worthy of trial.

Two chemical compounds have recently been studied that produce hypotension by acting directly upon the autonomic nervous system. *Tetrathylammonium bromide or chloride*¹⁵ is a quaternary ammonium ion that inhibits the passage of nervous impulses through the ganglia.

of the autonomic nervous system. Its action on the sympathetic nervous system predominates, thus giving rise to a generalized vasodilation resulting in a marked drop in both systolic and diastolic blood

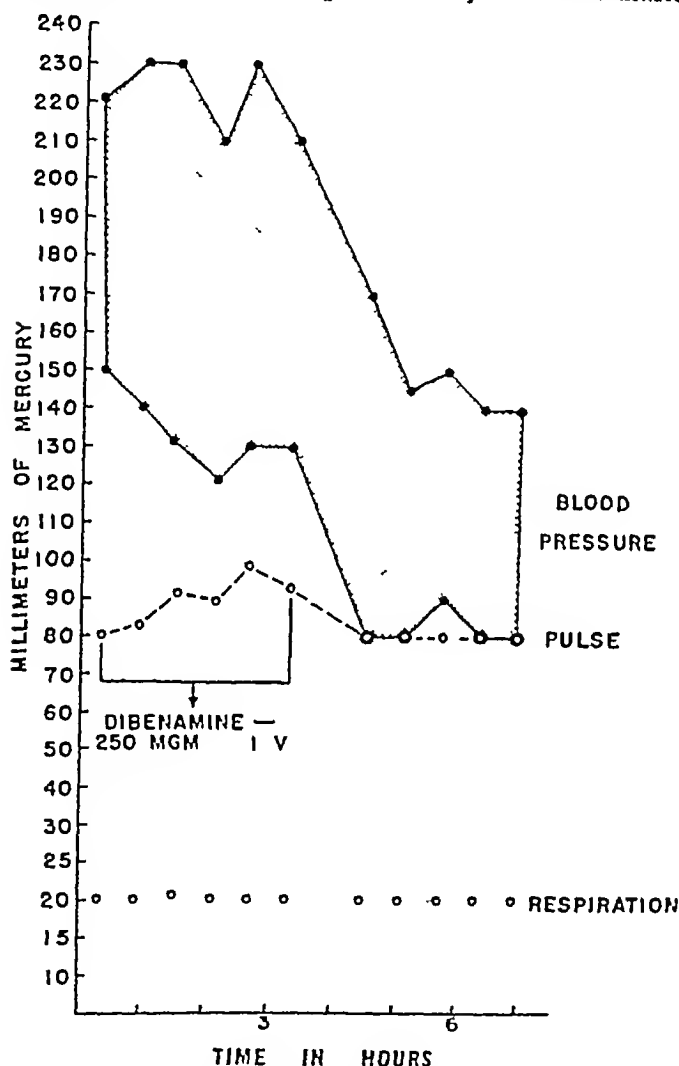


Fig 184 —Blood pressure response of C B, aged 27, after the slow intravenous injection of 250 mg of N, N-dibenzyl β -chloroethylamine (dibenamine) (Courtesy of Dr Fiorindo Simone)

pressures. The duration of the blood pressure fall when this substance is administered intravenously, is about eight hours (Fig 183). In addition to lowering the blood pressure in hypertensive patients, it is

definite hazard to the child Here is a great educational task of which few laymen and not all physicians are aware

A periodic and complete examination of the child should be made in accordance with the following schedule

- Birth to one year—monthly
- One year to six years—quarterly
- Six years to twelve years—semi-annually
- Twelve years to maturity—annually

The annual examination should include a roentgenogram of the thorax and a complete blood count and smear

There are suggestions—very striking suggestions—to be obtained at times when eliciting a history These are

First Changes in physique—either general or local, changes in disposition, habits, social adjustment or physical or mental accomplishments

Second (a) Unusual symptoms, (b) persistence of a group of common symptoms, (c) *periodic* episodes of ill health or behavior difficulties

Third (a) Swelling or “lumps” of nontraumatic nature, (b) failure of traumatic swellings to regress in the usual manner

By a careful history and thorough physical examination the great majority of cancers may be diagnosed promptly and with certainty

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reported to give temporary relief from headaches, impairment of vision dyspnea and orthopnea ¹⁵ *Dibenamine* (N, N-dibenzyl- β -chloroethylamine) ¹⁶ blocks the passage of nervous impulses in the sympathetic nervous system, probably by acting directly upon the effector cells to prevent response to epinephrine or sympathin E. It has a longer period of action than tetraethylammonium (Fig 184)

Both compounds have unpleasant side reactions which will have to be eliminated before it is wise to use them in the clinical treatment of hypertension.

SURGICAL TREATMENT: SYMPATHECTOMY

At present this is the most satisfactory method available for treating serious hypertension, but even in the best surgical hands it has limitations. There are five types of sympathectomy.

1 *The subdiaphragmatic splanchnicectomy of Craig and Adson* ^{17, 18} In this two-stage operation the splanchnic bed is denervated bilaterally (ten days apart) by a subdiaphragmatic resection of the splanchnic nerves, including a portion of the celiac and the upper two lumbar ganglia.

2 *The supradiaphragmatic sympathectomy of Peet*.¹⁹ This operation is a one-stage procedure and consists of the bilateral removal of the lower thoracic sympathetic ganglia and the intervening trunk, together with as long a segment of the great splanchnic nerve as possible. Convalescence is shorter than with the other procedures.

3 *The thoracolumbar splanchnicectomy or lumbodorsal sympathectomy of Smithwick* ²⁰ In this two-stage operation the lower four or five dorsal sympathetic ganglia, their intervening trunks, the splanchnic nerves and the first lumbar ganglion are removed bilaterally. Sometimes the second and third lumbar ganglia are also removed. The operation is followed by postural hypotension which may be severe if the second lumbar ganglion is removed. Convalescence is longer after this operation.

4 *The total thoracic sympathectomy* has been found by Smithwick²¹ to have been helpful recently in a limited number of hypertensive patients with tachycardia or angina pectoris.

5 *The subtotal or "total" paravertebral sympathectomy of Grimson* ²² The "total" operation consists of a transthoracic and abdominal resection of the sympathetic chains including the stellate ganglion, both thoracic chains, the celiac ganglion and the first and second lumbar ganglia.

Indications for Sympathectomy.—These are ill-defined. Factors that seem to be important in judging whether a sympathectomy will be of value in the treatment of a given case of hypertension are as follows: age, sex, the state of renal function, the magnitude of the pulse pressure, the response of the circulatory system to cold and

posture tests as measured by changes in the blood pressure, the sedation test, and lastly the presence of pyelonephritis

1 *Age*—Ordinarily patients under 50 years of age do better than those 50 or over. However, there are exceptions to this rule, and these seem to be in patients that look younger than their stated age

2 *Sex*—Women obtain greater benefit from a sympathectomy than do men

3 *Renal Function*—If the nonprotein nitrogen is elevated beyond 40 mg per 100 cc or the phenolsulphonephthalein test shows the excretion of less than 15 per cent dye in fifteen minutes in the absence of congestive heart failure the patient will not be helped by sympathectomy and may be hurt. In this respect dogmatism is justifiable

4 *Pulse Pressure*—Patients with small pulse pressures respond better than those with wide pulse pressures²³

5 *Response of Blood Pressure to the Cold Pressor Test (Cold and Posture Test)*.—Patients manifesting a considerable pressor response from standing or from putting their hand in ice water after resting for forty-eight hours in bed are likely to be helped by a sympathectomy. The converse of this statement is also true

6 *Sedation Test*—The diastolic blood pressure should drop to 110 or lower following the administration of sodium amytal as a forecast of success²³

7 *Pyelonephritis*—For some unknown reason patients with a history of pyelonephritis respond better than any other group of hypertensives

The history of a cerebral vascular accident, of myocardial infarction, or of slight angina pectoris does not contraindicate sympathectomy for hypertension. Following myocardial infarction it is best to delay the operation for at least three months to allow ample time for a readjustment of the coronary circulation. If congestive failure is present this should be treated with digitalis, diuretics and a low sodium regimen if necessary, and compensation restored before the operation is undertaken

Results of Sympathectomy.—An adequate consideration of these results should involve the following points

- 1 How many patients feel better after sympathectomy?
- 2 Are they able to carry on more activity postoperatively?
- 3 What is the cardiac evaluation after operation?
- 4 What changes, if any, occur in renal function after operation?
- 5 Is there any change in cerebral function postoperatively?
- 6 In a careful appraisal of blood pressure, what are the changes after operation?

It is generally stated by surgeons that patients are much better following sympathectomy, but no statistical study has been made with respect to the patient's subjective feelings, nor his activity following the operation. With regard to cardiac evaluation, the only follow-up

studies available are those dealing with the electrocardiogram before and after sympathectomy^{24, 25} These studies indicate that frequently there is an improvement in the electrocardiogram in hypertensive patients following the lumbodorsal sympathectomy, and that this improvement lasts for several years (Fig 185) That these changes do not take place in hypertensive patients following nonspecific operations has been shown by Rojas and his co-workers²⁶

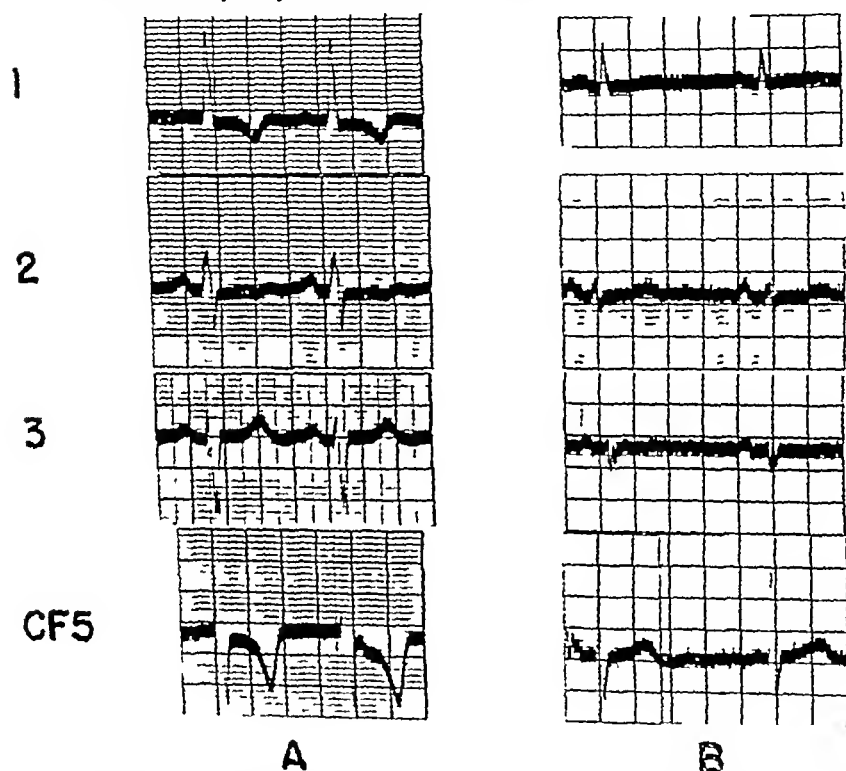


Fig 185—Reversal of the hypertensive electrocardiogram pattern after lumbodorsal sympathectomy in A M., a woman aged 49 A, preoperative electrocardiogram, taken November 12, 1943 Blood pressure 194/127 Sympathectomy, right, November 3, 1943, left, December 11, 1943 B, Over three years after sympathectomy Blood pressure 128/88 In this case the electrocardiogram has improved, but is still slightly abnormal.

Pect² believes that the renal blood flow increases following sympathectomy, and that renal function is improved. If we are justified in concluding that the retinal arterioles are representative of the arterioles in the brain, we may infer that the cerebral circulation is also improved following a sympathectomy Whether the incidence of cerebrovascular accidents is changed after sympathectomy is not known

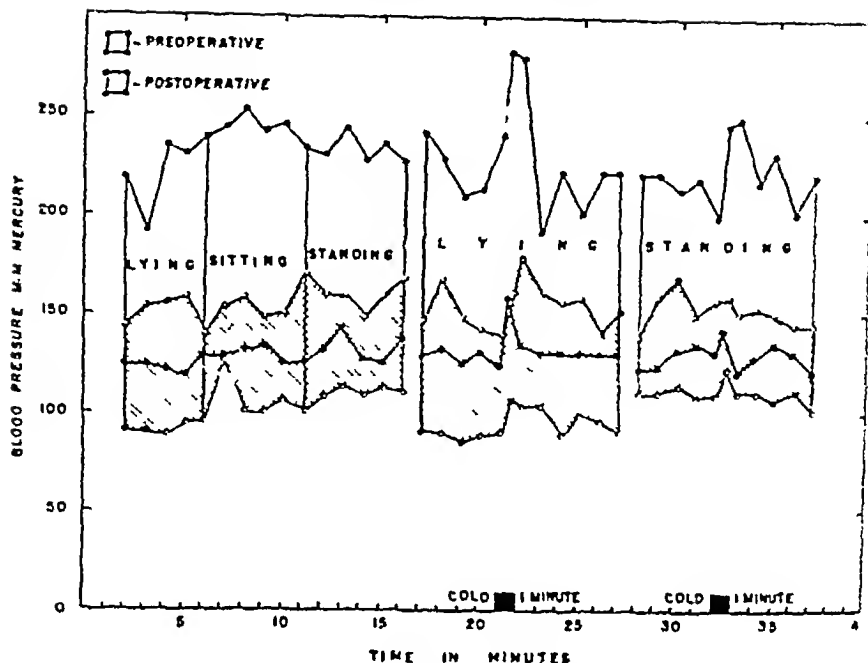


Fig 186—Cold and posture test, chart showing systolic and diastolic blood pressure readings before (upper record) and forty-five months after sympathectomy (lower record) Blood pressure recorded at the beginning in the basal state each minute for five minutes, first in the lying position, then in the sitting position, then in the standing position, then in the lying position before putting one hand in ice water for one minute and for five minutes afterwards, and then repeating this procedure in the standing position, in K. T., female, aged 46 years. Response to sodium amytal sedation, 146/92

BLOOD PRESSURE DATA

			Lying	Standing	Lying Response to Cold	Standing Response to Cold
Preoperatively			227/123	230/115	281/158	250/144
Postoperatively			150/91	159/111	177/104	160/124
	Cardiac Function	Renal Function	Brain	Eyes	Renal History	Muscle History
Preoperatively	Slight failure	Normal	Normal	Gr III	Chronic lateral pyeloneph- ritis	Normal
Postoperatively	Improved	Normal	Normal	Gr II		

The blood pressure may be reduced considerably in a few patients for as long as twelve years (Figs 186 and 187). In 189 unselected

cases followed from one to five years²⁷ the blood pressure was appreciably lowered in 65.8 per cent, unchanged in 12.8 per cent, and higher in 6.8 per cent, 14.6 per cent of this group of patients had died. In 319 selected cases followed from one to five years by the same author, 84.8 per cent showed an improvement of their blood pressure, 11.6 per cent were unchanged, and in 2.4 per cent it was higher, 1.2 per cent of this group died. Of the 120 cases excluded in this series 15.8 per cent had an improvement in their blood pressure, 15.8 per cent were unchanged, and in 16.7 per cent it was higher, 51.7 per cent of this group had died.

Complications of Sympathectomy.—Postural hypotension and shortness of breath are frequent complaints for about six weeks post-operatively, and may persist for years. These are seen most frequently in patients having a lumbodorsal sympathectomy. Back pains around the incisions, and pains in the abdomen due to nerve degeneration are present in all patients, and may persist for six months or a year. Excessive perspiration from the undenervated areas is bothersome directly after the sympathectomy, but this rarely lasts longer than six months. In winter the hands are very cold, necessitating warm gloves. On the other hand, the feet are frequently warm. In males, if the second lumbar ganglion is removed bilaterally nearly all patients lose their power of ejaculation. This is preserved in most cases if only the first lumbar ganglion is removed bilaterally.

Illustrative Cases.—The following two cases illustrate some of the problems encountered in the selection of patients for treatment by sympathectomy, and the use of certain tests that are helpful in appraising their hypertension.

CASE I.—R. H., a 44 year old man, was admitted to the Massachusetts General Hospital in 1944 with a complaint of dizzy spells for twelve years.

Present Illness. He was well until twelve years ago when he developed transient spells of dizziness, associated with dull headaches, without true vertigo. These increased in frequency and several months before admission they were occurring ten to twenty times a day, persisting at this frequency until his entrance to the hospital. His blood pressure was found to be high.

Six months prior to admission the patient noted increasing exertional dyspnea and paroxysmal nocturnal choking spells lasting thirty to sixty minutes and accompanied by severe coughing spells. Following such episodes he was so orthopneic that he had to sleep upright in a chair.

Five months before admission his exertional dyspnea became worse. Ankle edema developed. Shortly afterward he was admitted to the Peter Bent Brigham Hospital where it was noted that his liver and spleen were enlarged. He was digitalized and given ammonium chloride and mercupurin.

Past History. Scarlet fever at 11 years. No kidney disease or rheumatic fever.

Family History. Mother living and well at 78 years. Father died in 1917 from a "shock." Brother died of tuberculosis at 23 years. Another brother died from an unknown cause. Sister died of typhoid fever at 32 years. Another sister died from an unknown cause at 53 years.

Physical Examination On the patient's admission to the Massachusetts General Hospital, August 14, 1944, the physical examination showed a well developed, well nourished male with normal color. His neck showed no venous distention or venous pulsations. The fundi showed diffuse narrowing of the arterioles. No arterio-venous compression points, hemorrhages, exudates or papilledema were present. The pulse was regular at 62, and of good quality. Blood pressure was 240/130. On examination of the heart the apex beat was felt 11.5 cm. to the left of the midsternal line. The midclavicular line measured 8 cm. to the left of the midsternum. The rate was 60, the rhythm normal. The second aortic sound was louder than the second pulmonic sound, but not markedly accentuated. The first sound was split. The lungs were clear and resonant. The abdomen revealed no palpable organs and no masses. There was minimal pitting edema of the ankles.

Laboratory Findings The urine was negative for albumin, red blood cells, white blood cells, and casts. The red blood cell count was 5.8 millions, the white blood cell count was 12,200, the hemoglobin was 16 gm. A differential white blood cell count revealed 82 per cent polymorphonuclear leukocytes, 13 per cent lymphocytes, 1 per cent monocytes, no basophils, 1 per cent eosinophils. Platelets were normal. The urine concentrated to 1.028 when fluids were withheld for sixteen hours. A phenosulphonophthalein test showed excretion of 15 per cent dye in fifteen minutes and 64 per cent at the end of two hours. The nonprotein nitrogen was 29 mg. per 100 cc. of blood and the total protein was 6.4 gm. The Hinton test was negative. An electrocardiogram revealed a normal rhythm at 65, P-R interval 0.18 seconds, sagging ST segments in Leads I and II, inverted T waves in Leads I and II, and upright T waves in Lead III. There was moderate left axis deviation. The T waves were upright in Lead CF₂, diphasic in Lead CF₄, and inverted in Lead CF₅. It was felt that these changes were consistent with hypertensive heart disease and the action of digitalis. An x-ray film of the chest showed clear lungs, enlarged heart and tortuous aorta.

Blood Pressure Studies *Sedation Test* After three doses of sodium amytal, 0.2 gm. at hourly intervals, the blood pressure fell from 220/138 to 108/60. *Cold and Posture Test* (see Fig. 5) The effect of this test certainly was not marked. *Intravenous Pyelogram* The urinary tract was essentially negative.

Hospital Course Continuing the digitalis, the patient was given ammonium chloride 4 gm. a day, and two injections of mercuiprin 2.2 cc. two days apart which were followed by a 5 pound loss of weight. On August 23, 1944 a right lumbar dorsal splanchnicectomy was performed. The greater splanchnic nerve and the sympathetic chain from the first lumbar ganglion to the eighth thoracic ganglion were removed. Eight days later the left sympathetic chain from the second lumbar ganglion to the eighth thoracic ganglion was removed. As is the custom, immediately following this procedure the patient was given two transfusions, 500 cc. each of whole blood. He stood both operations well and showed a good lowering of his blood pressure. Eleven days after the second stage an electrocardiogram showed an improvement in the T waves of Lead II and the T waves in Lead CF₄. At his discharge, September 15, 1944, blood pressure in the horizontal position was 131/92 and 90/54 while standing. Although the patient complained of no postural hypotensive symptoms (dizziness, shortness of breath) the usual measures to combat them were used: a snug wrapping of both legs with ace bandages and the use of an abdominal binder in which rubber pads are fitted to exert pressure over the common iliac veins, preventing blood pooling in the lower extremities when the patient stands erect. It is usually necessary to wear the leg bandages for about six weeks until the denervated arteriolar bed has regained some of its muscle tone. The girdle is frequently worn for a longer period of time both to prevent the postural hypotension and to support the back.

Convalescence During the four months of recovery the patient complained of

only slight tenderness about the operative incisions. All medication was omitted two months postoperatively. The chart (Fig 187) illustrates the marked lowering in blood pressure twenty-eight months postoperatively (from 207 mm systolic and 127 diastolic to 135 systolic and 93 diastolic in the basal state recumbent)

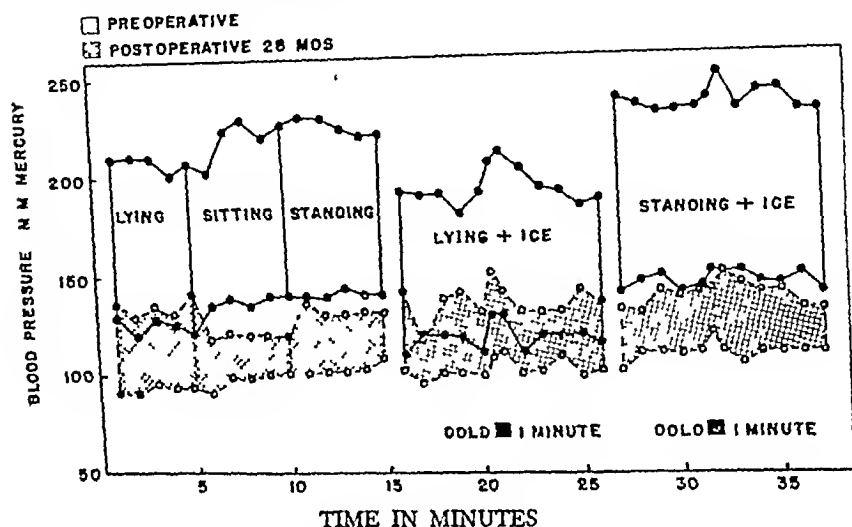


Fig 187—Cold and posture test chart showing systolic and diastolic blood pressure readings before (upper record) and twenty-eight months after sympathectomy (lower record). Blood pressure recorded at the beginning in the basal state each minute for five minutes, first in the lying position, then in the sitting position, then in the standing position, then in the lying position before putting one hand in ice water for one minute and for five minutes afterwards, and then repeating this procedure in the standing position, in R. H., male, aged 44 years. Response to sodium amytal sedation 108/60.

BLOOD PRESSURE DATA

	Lying	Standing	Lying-Response to Cold	Standing-Response to Cold
Preoperatively	207/127	224/140	212/130	248/152
Postoperatively	135/93	132/103	152/112	150/112

	Cardiac Function	Renal Function	Brain	Eyes	Renal Biopsy	Muscle Biopsy
Preoperatively	Congestive Failure	Normal	Normal	Gr I	Gr III	Normal
Postoperatively	Normal	Normal	Normal	Normal		

The paroxysmal nocturnal dyspnea, the orthopnea, the exertional dyspnea, and the ankle edema have disappeared. Physical activity has increased. The patient now can do moderately heavy farm work, nine hours a day, six days a week. An examination of the ocular fundi twenty-eight months postoperatively revealed normal

arterioles, no hemorrhages or exudates, and no papilledema. The urine showed no albumin, sediment was negative. A phenolsulphonephthalein test showed the excretion of 45 per cent dye in fifteen minutes, which is well within normal limits. The electrocardiogram is within normal limits now.

The operative complications were cold hands, increased perspiration over the upper portion of the body, diminution of libido and loss of ejaculation.

CASE II—This illustrates the type of hypertension that should not be treated by sympathectomy. R. W., a 43 year old male shipyard worker, was admitted to the Massachusetts General Hospital, June 22, 1945, with the chief complaint of swelling of the ankles.

Present Illness The patient had been perfectly well until three months ago when he developed a sore throat and a temperature of 103° F. Shortly after the onset of the sore throat a generalized rash appeared, diagnosed by his local physician as scarlet fever, and was followed by desquamation of the skin from both hands and feet two to three weeks later.

Five weeks after the onset of illness the patient noted swelling of legs and ankles, occasional nausea and vomiting, headaches, hazy vision, and nocturia three times a night. The local physician detected an elevated blood pressure and albumin in the urine. There was no history of dyspnea on exertion, orthopnea or chest pain.

Past History This was negative for previous attacks of kidney disease, rheumatic fever or any other severe illness.

Family History Both father and mother had died of undetermined causes at unknown ages. One sister was in a mental hospital. Another sister, 16 years of age, was living and well.

Physical Examination On admission the physical examination showed a well developed, well nourished male, not in acute distress. The pulse was 70, of good quality. Blood pressure was 250/130. Fundi revealed slight papilledema, spasm and narrowing of the arterioles. There were many areas of exudate and one area of hemorrhage was seen in the right fundus. The neck showed no venous pulsation or venous distention. On examination of the heart the apex beat was felt 3 cm. to the left of the left midclavicular line, which measured 10.5 cm. to the left of the midsternum. The rate was 70 and the rhythm was regular. The sounds were of good quality, A₂ greater than P₂. There was a Grade 2 apical systolic murmur transmitted throughout the precordium. The lungs were clear and resonant. The abdomen was negative for palpable organs and masses. There was moderate pitting edema of both ankles.

Laboratory Findings Urine revealed a 1 plus albumin. The sediment was loaded with red blood cells and showed many granular casts. There were 18 to 20 white blood cells per high powered field. Specific gravity ranged from 1.015 to 1.009 on the routine urine specimens. Red blood cell count was 1.2 million, white blood cell count was 7.1 thousand, hemoglobin was 12.6 gm. The differential white blood cell count showed 61 per cent polymorphonuclear leukocytes, 30 per cent lymphocytes, 2 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. Platelets were present. Red blood cells appeared normal. The nonprotein nitrogen was 56 mg. and the total protein was 4.62 gm. per 100 cc. of serum, the albumin was 2.78 gm. and the globulin 1.84 gm. per 100 cc. Urea clearance was 13.6 per cent of normal. The urinary concentration test, with fluids withheld for sixteen hours, showed a concentration to only 1.014. The phenolsulphonephthalein test showed an excretion of only 5 per cent dye in fifteen minutes, 20 per cent dye in two hours. Cultures of the urine were negative. An electrocardiogram showed normal rhythm at 75, P-R interval of 0.13, normal axis upright T₁, T₂ and T₃, with normal complexes and time intervals in the precordial leads CF₂, CF₄ and CF₆. An x-ray film

of the chest showed clear lungs, heart shadow slightly increased to the left, and a prominent curve of the left ventricle

Blood Pressure Studies Sedation Test After three doses of sodium amytal, 0.2 gm at hourly intervals, the blood pressure fell from 260/150 to 140/80 **Cold and Posture Test** This was not done because of the patient's illness **Intravenous Pyelogram** This revealed kidneys normal in size and shape Urinary passages were incompletely filled, excretion of dye was diminished in concentration and delayed, but there was a moderate amount of dye in the bladder forty-five minutes after the injection of dye These findings were interpreted as suggesting bilateral impairment of kidney function

It was believed that the patient was suffering from subacute glomerulonephritis and malignant hypertension.

Hospital Course A right lumbodorsal splanchnicectomy was performed on August 7, 1945 The greater splanchnic nerve and the sympathetic chain from the second lumbar ganglion to the eighth thoracic ganglion were removed On August 17, 1945 the same procedure was performed on the left side. The left kidney was completely decapsulated during the second operation A biopsy of the right kidney revealed chronic glomerulonephritis Although his edema improved somewhat following the sympathectomy, his blood pressure failed to decrease appreciably The patient was discharged on August 31, 1945

Following discharge the patient showed considerable azotemia and developed a pronounced anemia Four months postoperatively pulmonary infarction occurred and the patient died four days thereafter

This patient showed evidence of marked impairment of renal function preoperatively and should have been treated by dietary measures rather than by sympathectomy

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BONE MARROW EXAMINATION IN BLOOD DISORDERS OF INFANTS AND CHILDREN

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EXAMINATION of the bone marrow by sternal puncture constitutes a useful laboratory aid in the diagnosis of blood dyscrasias. The accessibility of the sternal marrow, its response to stimuli producing depression or hyperplasia, availability for repeated examinations, and the comparative ease of identifying the cellular elements account for the increasing frequency with which this procedure is performed. In younger patients where the blood picture may be obscured by the physiologic changes incident to growth and development, disturbances in the hematopoietic system may be more accurately appraised when the peripheral blood is examined in conjunction with the bone marrow.

Disturbances of each of the principal blood elements are frequently reflected earlier or are more conspicuous in the bone marrow than in the peripheral blood. This disparity is illustrated by the observation that in leukemia the bone marrow may be extensively infiltrated with leukoblastic cells which appear in the peripheral blood in such scant numbers as to be overlooked. In the hypoplastic and hemolytic anemias, bone marrow studies permit quantitative estimation of the cell types involved in the disorder. Bone marrow examination serves as a guide to therapy with anti-anemia agents by permitting observation of their effects upon maturation of the earlier red cell forms. The indications for the administration of folic acid, for instance, in the syndrome of megaloblastic anemia of infancy which recently was described¹ are better controlled with the aid of bone marrow studies.

The need for careful study of alterations in the white cells has increased since the advent of drugs known to produce agranulocytosis such as the sulfonamides and thiouracil. The effect upon hematopoietic organs and the possible value of therapy in restoring the white cells to normal levels are more accurately determined by study of the parent cells in the sites of origin. In addition to direct inspection of the precursors of the red and white cells, the examination of the bone marrow permits a study of platelet formation. In intrinsic hemorrhagic disorders it permits not only an estimate of the reaction of bone marrow to the loss of blood but direct observation of megakaryocytic con-

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THE MANAGEMENT OF PATIENTS WITH MASSIVE HEMORRHAGE FROM PEPTIC ULCER

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THE management of massive hemorrhage from peptic ulcer presents a challenge to both the internist and the surgeon. Every patient admitted to the hospital with a massive hemorrhage from the upper gastrointestinal tract may be considered a potential fatality. This applies particularly to patients over 50 years of age. The source of the hemorrhage should be determined, whenever possible, and the proper treatment instituted without delay. The state of shock, circulatory collapse and the response to treatment must be evaluated repeatedly in determining the course of management. In no situation are sound clinical judgment and the constant observation and re-evaluation of the status of the patient more essential than in the management of patients with acute massive hemorrhage from peptic ulcer.

DIAGNOSIS

The establishment of a definitive diagnosis is of paramount importance in the management of patients with acute massive hemorrhage from the upper gastrointestinal tract. In most instances the patient is admitted to the hospital because of hematemesis or the passage of tarry stools associated with the sudden onset of dizziness, perspiration, weakness and tachycardia, depending upon the severity of the bleeding and the acuteness of the blood loss.

Peptic ulcer is the most common cause of massive hemorrhage from the upper gastrointestinal tract. The history of active ulcer symptoms preceding the hemorrhage with the sudden cessation of all pain after the onset of bleeding justifies the tentative diagnosis of peptic ulcer. A previous diagnosis of peptic ulcer or the history of chronic intermittent ulcer distress over a period of years with recurrence of discomfort shortly before the onset of hemorrhage indicates a peptic ulcer as the probable source of the hemorrhage. Previous episodes of hematemesis or melena suggest the probability of peptic ulcer on a statistical basis because approximately 75 per cent of all massive hemorrhage into the upper alimentary tract is caused by peptic ulcer.¹

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Objective evidence of peptic ulcer obtained by previous roentgenologic examination is exceedingly valuable, not only in establishing the diagnosis but in localizing the lesion to the exact site in the stomach or duodenum. The finding of a deformity of the duodenal bulb, the visualization of an ulcer crater in the duodenum or the demonstration of a gastric ulcer niche on previous occasions in a patient who presents himself with hemorrhage from the upper gastrointestinal tract may be considered presumptive evidence of a recurrent hemorrhage from an ulcer.

Approximately 25 per cent of patients, however, deny the existence of ulcer symptoms prior to the hemorrhage. This is particularly true in the older age group. Not uncommonly the patient presents no history or roentgenologic evidence of a previous peptic ulcer, and studies performed in one fourth of the cases of massive hemorrhage within three weeks of the onset of the hemorrhage fail to establish the cause and site of the bleeding.

The source of the hemorrhage in many of these patients may be a hypertrophic gastritis, an erosive hemorrhagic gastritis or superficial gastritic ulcerations rather than a peptic ulcer. Massive fatal hemorrhage may result from gastritis, particularly hypertrophic gastritis. Hypertrophic gastritis and gastritic erosions are not uncommon, moreover, in the ulcer-bearing stomach. Patients with peptic ulcer, therefore, may be bleeding from an associated gastritis as well as from the active ulcer itself.

Esophageal varices, cancer of the stomach, gastric polyps, diaphragmatic hernia with a localized gastritis or gastritic ulcerations, and blood dyscrasias must be considered in the differential diagnosis of hemorrhage from the upper gastrointestinal tract.

The presence of esophageal varices secondary to portal hypertension may be suspected from the observation of jaundice, spider angiomas, ascites or the finding of a palpable liver or spleen. A history of chronic alcoholism in some of these patients may be significant. Cancer of the stomach is not a common cause of massive gastric hemorrhage and usually occurs in the late stages of an ulcerating carcinoma. Evidence of weight loss and the finding of an abdominal mass suggest the diagnosis.

Polyps of the stomach and other benign tumors may cause massive hemorrhage without warning. The diagnosis may be established by roentgenologic or gastroscopic examination. Hematemesis or melena in an elderly stout woman suggests a hiatus hernia, particularly in the absence of typical ulcer symptoms. The hemorrhage is initiated in these instances by gastritic erosions, ulcerations or severe hypertrophic gastritis within the herniated pouch. Blood dyscrasias should be suspected whenever multiple sources of hemorrhage are observed or splenomegaly of undetermined origin is found.

In those instances where the diagnosis is uncertain or the source of bleeding is not established, early roentgenologic examination may be valuable, particularly in those patients in whom early surgery may be necessary.² The localization of the ulcer by Hampton's technic³ and the demonstration of esophageal varices or a hiatus hernia are helpful in planning the management of patients with massive hemorrhage from the upper gastrointestinal tract.

Good clinical judgment is most essential in the selection of bleeding patients for early roentgenologic examination. The procedure is contraindicated in patients during shock and should be avoided, if possible, until the active massive bleeding has subsided.⁴ It is preferable to wait twenty-four to forty-eight hours after an acute massive hemorrhage before performing the roentgenologic examination of the stomach. In our experience, no untoward effects have been observed in patients undergoing early roentgenologic examination under these conditions.

If the source of the hemorrhage is known from a previous examination, or if the diagnosis can be established definitely from the history or physical examination, the roentgenologic examination should be postponed until the bleeding has stopped.

LABORATORY STUDIES

As soon as the patient with massive hemorrhage is admitted to the hospital, the state of shock, hemorrhage and dehydration should be evaluated and treated. The blood type, including the Rh type, is determined and donor bloods are crossmatched with the blood of the patient.

The severity and course of the hemorrhage are followed by repeated hemoglobin, red blood count and hematocrit determinations. Not infrequently the initial blood count and hematocrit readings are normal. The erythrocyte count, hemoglobin concentration and hematocrit determination do not always drop immediately after the hemorrhage because hemorrhage occurs at the expense of both the plasma and corpuscles, resulting in a markedly diminished blood volume. The restoration of the plasma volume depends upon the availability of water and electrolytes in the tissues. The fall in hemoglobin percentage and hematocrit determination following hemorrhage depends upon the restoration of the plasma volume, which, in turn, is related somewhat to the state of hydration of the patient. Thus, an uncompensated fall in blood volume in the dehydrated patient following a massive hemorrhage may not manifest itself until the plasma volume is restored. The magnitude of the hemorrhage becomes more obvious when the circulating blood volume is returned to normal by the administration of parenteral fluids. It may be necessary to determine

the hemoglobin and hematocrit values every four to six hours during the first few days of management to follow the course of the hemorrhage.

The leukocyte response to massive hemorrhage may be followed by repeated white blood counts. The blood platelet count, prothrombin time and bleeding and clotting time should be determined routinely, particularly if liver-spleen disease or a blood dyscrasia is suspected. A low blood prothrombin time is not infrequently observed in patients with massive hemorrhage from an ulcer without appreciable liver disease as a result, presumably, from decreased blood flow and anoxemia of the liver secondary to the massive hemorrhage. The administration of vitamin K may be helpful in these cases. The serum bilirubin determination may be valuable in patients suspected of bleeding esophageal varices associated with cirrhosis of the liver.

All stools and vomited gastric contents should be examined for gross and occult blood as an aid in evaluating the extent and the course of the hemorrhage.

Repeated plasma protein determinations are indicated in the presence of massive hemorrhage, pyloric obstruction, nutritional deficiency, peripheral edema or suspected liver disease. The blood urea nitrogen, blood chloride and carbon dioxide content of the blood are followed carefully, particularly in patients who have been vomiting or taking soluble alkalis. In these instances, alkalosis manifests itself by a decrease in the blood chloride and an elevation of the carbon dioxide content of the blood. The blood urea nitrogen is frequently elevated in patients with alkalosis on the basis of extrarenal azotemia. The blood urea nitrogen determinations are very significant, moreover, in the evaluation of renal impairment as well as the extrarenal azotemia of dehydration, shock and hemorrhage. These studies are indispensable in the management of patients with massive hemorrhage, particularly in the older age group. Not infrequently the elevation of the blood urea nitrogen is an index of the severity of the hemorrhage into the gastrointestinal tract and an expression of the alimentary absorption of digested blood.

BLOOD TRANSFUSIONS

There is considerable difference of opinion concerning the use of blood transfusions in the treatment of massive hemorrhage from peptic ulcer. Those who object to their use contend that blood transfusions do not affect the course of the hemorrhage and that further bleeding may be caused by the sudden elevation of the blood pressure. Another contraindication cited is the posttransfusion reaction.

Marriott and Kekwick,⁵ Gordon-Taylor⁶ and Wood,⁷ however, advocate massive transfusions. Jones⁸ employed this procedure in fifty cases with only one death, and concluded that massive transfusions

do not produce an appreciable rise in blood pressure and do not provoke further hemorrhage Browne and McHardy⁹ found no evidence of prolonged bleeding or elevation of blood pressures Crohn and Lerner,¹⁰ Miller,¹¹ Goldman¹² and Kruse¹³ present an intermediate viewpoint and recommend that transfusion be used cautiously and in small amounts Kirsner and Palmer¹⁴ found blood transfusions to be highly valuable in the treatment of severe hemorrhage and confirmed previous observations that the blood pressure is not raised significantly if the blood is given slowly

The indiscriminate use of blood transfusions, which overburden the circulating blood volume and prolong bleeding, should be avoided In our experience, however, repeated blood transfusions given slowly appear to be of definite value in the management of patients with acute massive hemorrhage from peptic ulcer Blood transfusions are effective not only in combating shock, exsanguination and hypoproteinemia, but they tend to exert a beneficial effect upon the course of the hemorrhage and the general welfare of the patient.

The patient's pulse and blood pressure should be recorded at half-hour intervals until the hemorrhage has been controlled Blood transfusions are administered to patients with massive hemorrhage when the systolic blood pressure falls below 100 mm Hg, when the pulse rate exceeds 120, and when the hematocrit determination falls below 28 or the hemoglobin below 10 gm per 100 cc No untoward effects have been observed from the transfusion of 500 cc of blood once or twice daily under these conditions if the blood is transfused slowly

It should be emphasized that the blood is administered slowly, at the rate of 4 cc. per minute, so that the transfusion of 500 cc requires approximately two hours Given over a two hour period, 500 cc of blood does not elevate the blood pressure significantly unless the patient is in shock. Under these conditions the blood pressure is increased gradually over the two hour period and rarely returns to the pre-hemorrhage level with one transfusion Transfusion reactions are not common if the blood is typed, crossmatched and the Rh type determined If insufficient blood is available, the intravenous administration of 500 cc. of plasma is indicated An intravenous infusion of 10 per cent glucose in saline may be initiated if the patient is in shock and neither blood nor plasma is immediately available

PARENTERAL FLUIDS

Parenteral fluids are required usually during the first forty-eight to seventy-two hours to help maintain the circulating blood volume, re-establish normal electrolyte balance and combat dehydration and azotemia Because of the danger of oliguria or anuria, particularly in the older patients with massive hemorrhage, it is essential to meas-

ure the urinary output daily and to maintain the renal output by administering sufficient parenteral fluids. The fluid and electrolyte requirements may be evaluated by the determination of the blood chloride, blood urea nitrogen and the carbon dioxide content of the plasma. If the patient is dehydrated and is suffering from chloride depletion as a result of vomiting or excess alkali therapy, the administration of water and chloride as physiological saline may be essential in establishing electrolyte equilibrium. On the other hand, the administration of excess fluids and sodium chloride may produce edema in the patient whose plasma proteins have been depleted. In these instances, if fluids are needed because of diminished renal output, dehydration or azotemia, glucose in distilled water may be administered. The hypoproteinemia should be treated with repeated blood or plasma transfusions.

The administration of excessive fluids should be avoided because of its effect in raising the blood pressure and increasing the circulating blood volume. This is particularly important in patients with massive gastric hemorrhage and cardiac decompensation. In these instances the administration of sodium and chloride is frequently contraindicated. Fluids may be given in the form of glucose in distilled water if necessary.

The total daily fluid intake should approximate 2000 to 2500 cc, depending upon the dehydration, azotemia, renal output, presence or absence of edema and the cardiac status of the patient. Fluids may be given as physiological saline, glucose in saline or glucose in distilled water and are administered by hypodermoclysis or by the intravenous route. Whenever intravenous fluid is administered, it must be given slowly, particularly in patients with heart disease.

DIET

The preliminary twenty-four to seventy-two hour period of starvation which was generally accepted as a basic part of the management of massive hemorrhage prior to 1935 is no longer preferable for the average patient unless he is in shock or complains of nausea or vomiting. The empty stomach neither prevents the secretion of acid gastric juice nor decreases gastric motility.

The present trend of therapy has been toward the immediate administration of small hourly feedings, if tolerated by the patient. This regimen has the advantages of maintaining the nutritional state of the patient, but is chiefly valuable in that it helps arrest the hemorrhage by reducing gastric acidity and decreasing gastric motility. Statistics indicate that the mortality rate is lower with this regimen than with that of the starvation management.¹¹ Most patients tolerate the diet well, and blood regeneration appears to be more rapid with this treat-

ment. If the patient is in shock, or if there is persistent nausea and vomiting, it is necessary to maintain an initial period of starvation until the patient is able to retain the feedings. This period usually does not exceed twenty-four to forty-eight hours.

The patient is given hourly feedings of 100 cc of milk and cream in equal parts from 7 A.M. to 10 P.M. During the night the schedule is continued at two hour intervals. The night feedings are particularly important because of the increase in gastric secretion during this period. The patient is awakened every two hours for the feeding and, if properly sedated, falls back to sleep immediately. If the patient is nauseated the cream is decreased or 100 cc of milk alone without cream is given. This regimen is maintained until the stools are negative for occult blood for three days. The usual routine of ulcer management is then instituted with supplementary small feedings, gradually increased to a three meal ulcer regimen within approximately two weeks.

The principle of this treatment is acid neutralization and gastric motor rest and relaxation. This dietary regimen has the advantages of the Meulengracht diet in that it supplies adequate nourishment to the patient and decreases gastric motility as well. It obviates the disadvantages of the Meulengracht regimen in that it does not increase the vigor and amplitude of gastric contractions and is less likely to stimulate the flow of a large volume of acid gastric juice.

The regimen of frequent small oral feedings of milk and cream has many of the advantages of the constant intragastric drip method in that it supplies a constant and uniform means of buffering the gastric juice without causing the discomfort and spasm not infrequently associated with the continuous intubation methods.

Intubation, in general, should be avoided in patients with massive gastric hemorrhage. Gastric siphonage may produce spasm and irritation of a gastric ulcer. It may provoke further bleeding, particularly in the presence of a chronic hypertrophic or chronic erosive hemorrhagic gastritis. Intubation is contraindicated if esophageal varices are suspected. Finally, prolonged intubation may favor the development of parotitis and pneumonia.¹⁴

ANTACIDS

The presence of highly acid gastric juice may increase the danger of persistent bleeding by favoring the extension of the ulcer process and by its destructive action on the fibrin clot which forms usually at the bleeding point. One of the most important problems in therapy is the achievement of as complete and constant neutralization of acid secretion as possible throughout the day and night. Although the milk and cream feedings result in a certain degree of acid neutralization,

further neutralization of the highly acid gastric juice may be advisable, particularly in patients with marked hypersecretion

Various antacids are in common use. Calcium carbonate, 2 to 4 gm hourly, is an effective antacid but tends to cause constipation, fecal impactions and alkalosis. The use of sodium bicarbonate is contraindicated because of the danger of alkalosis, particularly in patients who are vomiting. Shaw¹⁵ and Kruse¹³ favor the use of tribasic calcium phosphate and tribasic magnesium phosphate, while Woldman¹⁶ and Browne and McHardy⁹ advocate the administration of a continuous aluminum hydroxide drip as the best means of preventing fibrin clot digestion.

The addition of 5 to 10 cc of colloidal aluminum hydroxide to the hourly milk and cream feedings constitutes a very adequate and continuous form of antacid therapy and is used routinely in the management of patients with massive hemorrhage from the gastrointestinal tract. No significant complications other than constipation have been observed. In these instances, a small oil retention or tap water enema may be required.

SEDATION

Complete physical and mental rest is essential in the proper management of patients with massive hemorrhage. Reassurance, good nursing care and the judicious use of sedatives contribute appreciably to successful treatment. The choice of sedatives should conform with the individual requirements of the patient. In most instances the barbiturates alone are entirely satisfactory and no opiates are necessary. Sodium phenobarbital hypodermically (0.060 to 0.120 gm) every four to six hours is the sedative of choice. This sedative is particularly valuable when the patient is awakened at two hour intervals during the night for milk and cream feedings. When the sedatives are administered carefully during the night, the patient very frequently has no recollection of being awakened. If the patient is unusually apprehensive and restless, opiates may be helpful although they are rarely necessary. Morphine has been shown to exhibit an inhibitory effect on the fasting gastric secretion in man,¹⁷ but its tendency to cause nausea and spasm in some instances makes preferable the hypodermic administration at four to six hour intervals of dilaudid (0.002 to 0.004 gm), demerol (0.050 to 0.100 gm) or pantopon (0.010 to 0.020 gm).

The patient should be kept in bed until all signs of bleeding have disappeared, as evidenced by repeated guaiac-free stools and a stabilized blood hemoglobin of 11.5 to 12.0 gm per 100 cc or a hematocrit determination of 35 to 36.

ANTISPASMODICS

Atropine sulfate, in depressing vagal activity, may reduce both the motor and secretory activity of the stomach if given in adequate doses. The oral or parenteral administration of 0.6 mg three to four times daily, depending upon the individual tolerance of the patient, is of great value in controlling gastric secretion or spasm, and is particularly effective in the reduction of night secretion.

VITAMINS

Although there is no evidence that vitamin C deficiency is a cause of chronic peptic ulcer in man, secondary vitamin deficiencies may occur, particularly in ulcer patients with hemorrhage. Vitamin C deficiencies in patients with peptic ulcer have been reported.¹⁸ Portnoy and Wilkinson¹⁹ and Bourne²⁰ have demonstrated, moreover, a marked vitamin C deficiency in patients with bleeding peptic ulcer. We believe it advisable, therefore, to administer 100 mg of vitamin C parenterally daily during the acute phase of the hemorrhage and then to administer it orally until an adequate diet may be resumed.

In view of the fact that a marked posthemorrhagic prothrombin deficiency may exist in the absence of liver disease, the prothrombin time is determined in every patient admitted with gastric hemorrhage. This is particularly important in patients with massive hemorrhage associated with liver disease or with suspicion of liver-spleen disease. The intramuscular injection of 1 to 2 mg of vitamin K twice daily in ulcer patients with posthemorrhagic prothrombin deficiency results in a prompt restoration of the normal prothrombin time.

EMERGENCY SURGERY

The treatment of choice in the great majority of patients with acute massive hemorrhage from peptic ulcer is conservative medical management. The possibility, however, that the hemorrhage in any given instance may prove fatal without surgical intervention must be constantly borne in mind, particularly in patients over 50 years of age. The selection of those patients whose hemorrhage will be fatal without surgery from those whose hemorrhage will be controlled by medical management alone is often extremely difficult. Moreover, in many instances surgery may be delayed until late in the course of the hemorrhage when the patient becomes a poor surgical risk and is subject to a high mortality rate. Thus, Finsterer,²¹ Gordon-Taylor,⁶ Allen,²² Heuer²³ and others advise surgical intervention within twenty-four to forty-eight hours of the onset of the hemorrhage, since the mortality rate rises precipitously after this period. For this reason, all patients admitted to the Medical Service of the Peter Bent Brigham Hospital with acute massive hemorrhage from the upper gastrointestinal tract

are seen by the surgeons in consultation during the initial phase of the hemorrhage to avoid unnecessary delay if surgical intervention is found necessary. Surgical experience indicates that the simple ligation of the bleeding points is unsatisfactory because of the strong likelihood of secondary hemorrhage. Subtotal gastrectomy with removal of the ulcer is the procedure of choice in most instances.

The most careful individualization of the patient must be observed in selecting those for emergency surgery during the acute massive hemorrhage. To operate routinely in all cases of severe ulcer bleeding would result, we believe, in a mortality far greater than with medical treatment alone.^{1, 11, 14} Since the mortality rate, even among patients in the older age group, is in all probability considerably lower with conservative medical management than with emergency surgery,^{1, 14} the patient should be treated first by conservative means for twenty-four to forty-eight hours.

If the blood pressure continues to fall and cannot be maintained in spite of a strict medical regimen and adequate blood transfusions, immediate surgery should be contemplated. Emergency operation should be considered seriously if the patient has a massive and persistent hemorrhage which does not appear to be diminishing with treatment. This is particularly true if the patient is over 50 years of age and presents a long history of ulcer symptoms. The recurrence of a severe hemorrhage, with an associated fall in blood pressure, several days after the recovery from a massive hemorrhage constitutes another indication for emergency surgery.

The age of the patient is an important consideration when contemplating emergency surgery during the acute hemorrhage. Although the hemorrhage is more likely to be fatal in patients over 50 years of age, the general condition of the patient must be evaluated carefully. Each patient must be judged individually. The presence of cardiac decompensation, a recent coronary occlusion, severe hypertension, renal failure and marked obesity are relative contraindications to emergency surgery. In many such instances, a surgical fatality is averted by the continuance of strict medical management with the eventual recovery of the patient.

There are additional factors which may be considered before recommending emergency surgery. Fatal hemorrhages are less frequent among women than among men, and the statistical chance of recovery with medical management in either sex is better after multiple hemorrhages than with the initial hemorrhage.

The site of the hemorrhage is of considerable importance. The majority of bleeding duodenal ulcers are situated on the posterior wall and may present technical difficulties which contribute to a higher mortality rate if the operation is performed during the acute bleeding stage. Gastric ulcers, however, are dealt with surgically

definite hazard to the child Here is a great educational task of which few laymen and not all physicians are aware

A periodic and complete examination of the child should be made in accordance with the following schedule

- Birth to one year—monthly
- One year to six years—quarterly
- Six years to twelve years—semi-annually
- Twelve years to maturity—annually

The annual examination should include a roentgenogram of the thorax and a complete blood count and smear

There are suggestions—very striking suggestions—to be obtained at times when eliciting a history These are

First Changes in physique—either general or local, changes in disposition, habits, social adjustment or physical or mental accomplishments

Second (a) Unusual symptoms, (b) persistence of a group of common symptoms, (c) *periodic* episodes of ill health or behavior difficulties

Third (a) Swelling or “lumps” of nontraumatic nature, (b) failure of traumatic swellings to regress in the usual manner

By a careful history and thorough physical examination the great majority of cancers may be diagnosed promptly and with certainty

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more easily than duodenal ulcers. Finally, if the diagnosis cannot be established and the source of the hemorrhage has not been determined, emergency operation is contraindicated in most instances

ELECTIVE SURGERY

The question of elective surgery in patients who have recovered from a massive hemorrhage from peptic ulcer presents an important problem. Approximately 70 per cent of patients who have had two or more hemorrhages are likely to suffer from further hemorrhages. Thus, if the patient has had two or more massive hemorrhages from peptic ulcer, elective surgery should be contemplated if there are no specific cardiovascular or renal contraindications. This applies particularly to patients in the older age group. Elective surgery may also be indicated after a single massive hemorrhage, particularly if the patient has had a chronic peptic ulcer and has not been able to follow a strict medical regimen.

It is advisable in many instances to investigate gastroscopically the presence or absence of an extensive gastritis in patients with hemorrhage from the upper gastrointestinal tract. There is an appreciable incidence of recurrence of gastric hemorrhage in patients who have undergone a gastric resection for bleeding peptic ulcer.²⁴ In many of the instances, the remaining stomach may be involved in an extensive gastritic process. Gastritis may also explain the source of hemorrhage in the 25 per cent of patients in whom the roentgenologic examination does not establish the cause. Careful gastroscopic examination is indicated in these instances before surgery is undertaken.

DISCUSSION

The management of older patients with massive hemorrhage from peptic ulcer presents a difficult problem, as evidenced by the higher mortality rate in this age group. Six patients, 65 to 79 years of age, were admitted to the Peter Bent Brigham Hospital, within a two-month period, with massive hemorrhage from peptic ulcer (Table 1). Cardiovascular disease, cardiac decompensation, hypertension and urinary retention were the most commonly encountered associated diseases, as might be anticipated among patients of advanced age.

Patient I A, 69 years of age, had suffered a cerebral accident eighteen months prior to his gastric hemorrhage. His blood pressure had been recorded previously as 210/125 mm of mercury, and he was digitalized because of cardiac decompensation one year before his admission with a massive gastric hemorrhage. Patient G F, 79 years of age, presented the history of a previous coronary occlusion, cardiac decompensation and auricular fibrillation. Patient L B, 65 years of age, had an established blood pressure of 300/160 mm of

TABLE 1

MASSIVE HEMORRHAGE FROM DUODENAL ULCER IN PATIENTS 65 TO 79 YEARS OF AGE

Patient	Age	Source of Hemorrhage	Associated Diseases	Number of Previous Hemorrhages	Symptoms Immediately Prior to Hemorrhage	Number of Transfusions	Lowest Hematocrit	Disposition
I A	69	Duodenal ulcer	Arteriosclerotic heart disease, cardiac decompensation, hypertension, 210/120, cerebral thrombosis, benign prostatic hypertrophy	0	None	11	21	Medical management, recovery
W O	65	Duodenal ulcer	Arteriosclerotic heart disease, cardiac decompensation, auricular fibrillation	3	4 weeks	10	18	Medical management, recovery, surgery advised
G F.	79	Duodenal ulcer	Arteriosclerotic heart disease, coronary occlusion, auricular fibrillation, cardiac decompensation, Paget's disease, diverticulosis, benign prostatic hypertrophy	8	None	3	28	Medical management, elective gastric resection, recovery
L B	65	Duodenal ulcer	Hypertensive - cardiovascular disease, B p 300/160, cardiac decompensation, benign prostatic hypertrophy with urinary retention	2	None	1	26	Medical management, recovery
I J	67	Duodenal ulcer	Benign prostatic hypertrophy	1	6 weeks	2	21	Medical management, elective gastrectomy, recovery
C D	65	Duodenal ulcer	Rheumatic heart disease	8	None	15	21	Medical management, recovery, surgery advised

mercury prior to his gastric hemorrhage and had been suffering from chronic heart failure for several years. The importance of adequately digitalizing these patients and maintaining the blood volume and electrolyte balance without overburdening the circulation cannot be overemphasized.

Repeated blood transfusions, if administered slowly, may be given with relative impunity, as was noted previously. Eleven transfusions of 500 cc of blood were given over a period of nine days to patient I A with beneficial results, although the patient presented the history of hypertension, cerebral thrombosis and cardiac decompensation. Ten transfusions were administered successfully to patient W O over a period of eight days. This patient was admitted with chronic heart failure and auricular fibrillation of ten years' duration. Patient E D, 65 years of age, received fifteen blood transfusions over a period of ten days with the successful termination of the hemorrhage. Patient L B, with a blood pressure of 300/160 mm of mercury, required only one transfusion to control his hemorrhage.

That ulcer symptoms are frequently absent immediately prior to the hemorrhage, particularly in the aged, was illustrated in four of the six patients described in Table 1. Intermittent ulcer symptoms had existed in all these patients, however, for fourteen to thirty-seven years.

The diagnosis of duodenal ulcer was confirmed in all instances by roentgenologic examination after the hemorrhage had subsided. The additional diagnosis of hypertrophic gastritis was established in patients I A, G F and I J by gastroscopic examination or microscopic study of the resected stomach following surgery.

The patients were maintained on medical management until all evidence of bleeding had disappeared. The advisability of elective surgery several weeks after the hemorrhage had been terminated was considered in each case. A gastric resection was recommended for patient G F in spite of his advanced age, in view of the history of eight massive hemorrhages while the patient had been maintained on a strict ulcer regimen. The patient survived the operation. Elective surgery was advised and performed successfully in the case of patient I J, who had suffered four previous hemorrhages. Patients W O and E D were also advised to undergo elective surgery in view of their repeated hemorrhages.

Surgery appeared contraindicated for patient L B because of his severe hypertension and cardiac decompensation. It was not recommended in the case of patient I A, who had experienced only one hemorrhage in spite of the fact that his ulcer history extended over a period of thirty years and that he had never been instructed to follow an ulcer regimen. Marked obesity associated with hypertension and cardiac decompensation were additional factors in advising against surgery.

All patients who have experienced a massive hemorrhage from peptic ulcer, regardless of whether or not they have undergone surgery, should be observed and studied periodically. The incidence of recurrent hemorrhage justifies a careful and repeated therapeutic and diagnostic follow-up of these patients.

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TREATMENT AND PREVENTION OF CERTAIN COMMON SKIN DISEASES

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CERTAIN general principles in regard to treatment of cutaneous disease can contribute to their successful management. Likewise due consideration of the preventive aspects of these dermatoses can do much to decrease discomfort, limit disability and lessen the frequency of disease.

Because of the limitations of space only a few of the more common diseases will be discussed in this issue. The eczema-dermatitis group has been omitted because a reasonable consideration of them would more than fill the allotted space.

PRINCIPLES OF TREATMENT

1 The first essential is the correct diagnosis. It should be remembered that laboratory studies, biopsy, scale examination, culture, skin tests, and consultation are often necessary to arrive at the proper diagnosis before starting therapy, except for relief of symptoms.

2 The causal factors, if they can be ascertained, should be eliminated.

3 The proper therapy should be selected with due regard to the stage of the disease, the age of the patient, the site or sites of the disease, the previous treatment received by the individual, and perhaps the other diseases which the individual may have.

4 Overtreatment should be avoided, e.g., in acute irritations of the skin and in conditions where the diagnosis is uncertain, soothing or mild measures should be used.

5 Careful directions should be given in regard to the details of application of local agents and other therapeutic measures.

PRINCIPLES OF PREVENTION

1 The term "prevention" applies particularly to the prevention of extension of infections such as impetigo and scabies from one individual to another.

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2 The term also concerns the prevention of extension of disease in the afflicted individual and applies with equal force to infections and to acute dermatitis, especially where the individual's skin has become sensitized. It also concerns the early diagnosis and early treatment of such a disease as skin cancer in order to prevent its spread to neighboring tissue or organs.

3 The prevention of complications of a disease requires a knowledge of that disease, its etiological factors and accepted methods of treatment.

4 The prevention of the complications of cutaneous therapy needs further emphasis. They are much too frequent. More care should be taken to avoid these distressing complications on the skin, whether due to internal medication, to physical agents such as x-ray and ultraviolet light, or to external applications, especially of agents of unknown composition, or with known sensitizing agents, such as the sulfonamides or local anesthetics.

5 The term "prevention" should include the giving of careful directions to prevent the appearance of recurrences in those diseases in which there is the tendency to recur, insofar as those factors are known.

6 Prevention also applies to the matter of instructions which can be given to the individual in order to shorten the course or alleviate the symptoms of the disease. Thus there are several phases of prevention which are of value in the management of cutaneous disease.

ACNE VULGARIS

Systemic Therapy.—Since about three-fourths of adolescent boys and approximately one-half of pubescent girls develop some degree of acne, this disease is obviously related to endocrine imbalance in some fashion. If that function could be regulated properly, acne could doubtless be easily controlled. Efforts in that direction are rather unsatisfactory, but in some of the older acne age group the administration of female sex hormone in young women in the last one or two weeks of the intermenstrual period is often helpful.

The essential disturbance is hyperactivity of the sebaceous glands with alteration of the nature of the secretion. Excessive oiliness is the usual result and a reduction of fat intake is warranted. In some instances a marked reduction of fat is beneficial and in others a low carbohydrate intake will be useful. Chocolate has a particularly irritating effect on the sebaceous glands, as do also the iodides and bromides, all sources of these substances must be shut off. In a few cases where oiliness is supplanted by profuse comedo formation with keratosis of the follicular orifice, vitamin A may be of considerable value. Doses of 100,000 units or more daily can be given for several months at a time.

It is doubtful whether other systemic measures are of appreciable value except where the general medical condition requires attention. Correction of any chronic ailment, digestive disturbance, bowel stasis, anemia or malnutrition and sometimes the removal of foci of infection are in order. In short, the maintenance of good health is eminently desirable. An abundance of sleep, fresh air and exercise is recommended.

Local Therapy.—Topical measures should be varied in accordance with the type of acne presented. A thorough cleansing twice daily with any good soap is essential but trauma from unduly rough manipulation is undesirable. Sulfur soaps are frequently useful and soapless (sulfated oil) detergents are excellent. The oily tendency of the ovarian catamenia may be combated with drying lotions varying from common calamine mixtures to alcoholic suspensions of sulfur and camphor or the time-honored "lotia alba." The addition of resorcin may be advisable in some cases. Such agents are best applied at night only, if additional drying effect is required, borated alcohol may be used each morning. It is wise to start with a relatively mild lotion and increase its strength if necessary to keep the skin reasonably dry. Cream and ointments are ordinarily not suitable for the management of acne. In the infrequent cases with dry skins and profuse comedone formation, a 3 per cent salicylic acid cream is useful. Manual removal of blackheads is generally not to be advocated, the resultant trauma usually leading to more harm than good. Similarly, the evacuation of pustules must be carried out with most gentle manipulation and patients cannot be too stringently cautioned in this respect. Incision is not recommended except for the infrequent cystic acne. The application of heat is likewise to be avoided, aside from its use for occasional deep, indolent, indurated areas.

Many forms of adjuvant treatment have been recommended but they are in general rather disappointing. Such measures as vaccines, toxoids, bacteriophage, autohemotherapy, foreign protein injections, liver extract, tin and manganese seem to benefit only the exceptional patient. Ultraviolet radiation is more apt to be effective as a local approach in dark-skinned persons. Its benefit is usually transient and the skin builds up a tolerance to it if continued indefinitely. The value of general body exposure for a so-called tonic effect is dubious.

Roentgen radiation is without doubt the one form of treatment most effective in stubborn cases. It is not advisable in the early teens, in predominantly superficial involvement, or when the case is of the dry type, it is not effective in cystic acne. In properly selected patients, x-ray treatment provides the highest percentage of good results and the most lasting effect of any form of therapy, but training and experience are necessary for its proper employment. Fractional exposures to a total of two erythema doses (about 600 r) over a period of two

months or more, constitute a safe course of radiation. A single repetition of the series is warranted in some instances but under no circumstances must the ultimate total exceed four erythema doses. Sun exposure must be avoided during the time of x-ray treatment and local application should be reduced to the use of borated alcohol. Diet and other general therapy cannot be disregarded for six months to one year after success has been achieved.

Scarring produced by acne is extremely difficult to improve. Strong peeling agents and carbon dioxide slush have proved useful in some hands but are not generally advocated.

It is of more than passing importance to give heed to the scalp in acne patients. Seborrhea and acne are both sebaceous gland disturbances and each must receive attention when concomitantly existent.

Prevention.—It is especially useful to be alert for signs of acne in preadolescent youth when there is any appreciable familial tendency to this disease, or seborrhea. The aforementioned dietary suggestions can be instituted without effect on the nutritional requirements of growth and development. Vitamin A should also be useful at that stage. Sulfur soap and the salicylic acid cream should be sufficient topical approach since excessive oil is seldom an early manifestation.

ALOPECIA AREATA

Systemic Therapy.—The cause of this disease is unknown and its treatment is thereby entirely empiric. The patchy noninflammatory alopecia most commonly affects the scalp or beard but may occur on any hairy surface, or even result in complete loss of all body hair. A psychosomatic background may be used to explain many cases, but there are possible factors of endocrine imbalance, toxic states and dietary deficiencies in other instances. The self-limited and recurrent tendency of the disease casts doubt on all but the first of the possible causes listed. Therapeutic approach based on any of the aforementioned etiologic factors may be beneficial through its psychotherapeutic effect, even though the cause might have been psychic or emotional trauma.

It is doubtful that either hormonal or dietary therapy is of real benefit, barring actual indications for their use. Unless alopecia areata is extravagant and persistent, the removal of possible foci of infection seems a bit heroic, but in alopecia totalis any rational procedure may be warranted. A multitude of systemic remedies has been employed in the management of alopecia areata, including iron, arsenic, cod liver oil, vitamins, foreign protein injections and general ultraviolet exposures.

Local Therapy.—The employment of counterirritants has constituted standard approach to topical treatment. The production of liv-

peremia may be sufficiently stimulating to provoke activity in hair follicles, regardless of the cause of the cessation of hair growth. The areas may be painted with 95 per cent phenol, if of limited extent, and neutralized with alcohol in one or two minutes. Strong solutions of resorcin (20 to 30 per cent) in alcohol and ether may be applied. Tincture of iodine, followed by massage with ointment of ammoniated mercury, will provide adequate reaction. Blistering doses of ultraviolet radiation may suffice. Any such measure should be stopped when a local reaction takes place, it may be repeated as necessary after healing occurs. If the patient is of such temperament as to require daily treatment, milder applications should be ordered. This can include alcoholic lotions containing resorcin, cantharides, chloral and the like, and ointments of sulfur and salicylic acid or ammoniated mercury and salicylic acid.

Local vasodilatation can be produced also by iontophoresis with methylcholine and by the use of pilocarpine orally or by injection. The not infrequent occurrence of spontaneous cures of alopecia areata lead one to suspect that topical, as well as systemic, therapy may be effective mainly as psychotherapy.

Prevention.—Prophylactic measures for a disease of unknown cause are difficult to postulate. In alopecia areata, with its tendency to recur, it is occasionally possible to identify precipitating factors and keep the incidence to a minimum.

DERMATOPHYTOSIS

Dermatophytosis—"athlete's foot"—is a highly prevalent disease. The diagnosis should be proved by the microscope or culture since not all scaling lesions or erosions on the feet are caused by a fungus infection. In view of the amount of dermatitis seen in cases referred to the dermatologist following earlier treatment it is advisable that strong antiparasitic agents be used cautiously. The stage of the disease, its location, the amount and type of previous treatment—all make considerable difference in the treatment to be ordered.

Local Therapy.—In general it can be said that the more acute, more vesicular, more oozing cases should have frequent soakings of the feet, possibly with wet dressings of saturated boric acid solution, potassium permanganate 1:3,000 to 1:10,000, or Burow's solution (liq. aluminum subacetate), diluted 1:60 to 1:10.

Some mild antiseptic or antiparasitic powder, possibly borated talc, thymol iodide, or the newer Desenex or Sopronol powders should be used in the morning, and preferably an antiparasitic ointment at night. The fatty acid preparations referred to above are being used considerably more at present in place of the older Whitfield's ointment or ammoniated mercury ointment, 5 per cent. Five per cent mercurio-chrome, genitan violet 2 per cent, tincture of iodine, preferably 3:5

per cent, and Castellani's paint have all proved valuable in some cases. In the older, more chronic cases much difficulty is encountered in treatment. It is often necessary to continue with the more chronic types on a regimen that keeps the infection at a minimum.

Prevention—Frequent bathing of feet and the routine use of a powder to control moisture are of value for individuals with much perspiration. Feet should be protected when walking on bare floors of locker rooms and shower baths. The pools of antiparasitic solution to step into on the way to shower baths have not been particularly effective.

ERYTHEMA MULTIFORME

Systemic Therapy.—A syndrome or symptom complex is the correct designation for erythema multiforme, since it is not a disease entity but a symptomatic or toxic manifestation of morbidity elsewhere which is merely reflected to the skin. Treatment must be directed towards relief of the acute symptoms, and an active approach and etiologic factors delayed until recovery, lest a severe exacerbation be precipitated.

Should infection be identifiable, the use of penicillin or other suitable antibiotic would obviously be warranted. The cautious exhibition of sulfonamides might similarly be indicated. Many drugs are capable of producing erythema multiforme, however, and the sulfonamides are included, others are phenolphthalein, arsenic, salicylates and the halogens. They may serve more in the role of precipitating factors, but withdrawal is obviously indicated if they are being used at the onset of erythema multiforme. On the other hand, arsenic in various forms (Fowler's solution by mouth or sodium arsenate by injection) has long been used in treating erythema multiforme, and salicylates are frequently administered for symptomatic relief. Foods are occasionally blamed and it is not amiss to claim any suspected ingestants plus such urticariogenic foods as chocolate, shell fish, eggs, nuts, pork and berries. Daily intravenous injections, 5 to 10 cc of a 10 per cent solution of calcium gluconate or levulinate, will often provide much relief regardless of the cause. Autohemotherapy and intravenous sodium thiosulfate are also used.

The newer antihistaminic drugs, i.e., benadryl and pyribenzamine, may be dramatically effective but can also fail completely. They are eminently worth trying. Sedation with chloral or paraldehyde is not infrequently necessary where discomfort is severe. An increased fluid intake is of value.

Local Therapy.—Although a self-limited condition, erythema multiforme is an acute inflammatory eruption frequently affecting the mucous membranes as well as the skin, and topical measures which will afford relief are of major importance. For oral lesions, frequent

BONE MARROW EXAMINATION IN BLOOD DISORDERS OF INFANTS AND CHILDREN

CARL H. SMITH, M D *

EXAMINATION of the bone marrow by sternal puncture constitutes a useful laboratory aid in the diagnosis of blood dyscrasias. The accessibility of the sternal marrow, its response to stimuli producing depression or hyperplasia, availability for repeated examinations, and the comparative ease of identifying the cellular elements account for the increasing frequency with which this procedure is performed. In younger patients where the blood picture may be obscured by the physiologic changes incident to growth and development, disturbances in the hematopoietic system may be more accurately appraised when the peripheral blood is examined in conjunction with the bone marrow.

Disturbances of each of the principal blood elements are frequently reflected earlier or are more conspicuous in the bone marrow than in the peripheral blood. This disparity is illustrated by the observation that in leukemia the bone marrow may be extensively infiltrated with leukoblastic cells which appear in the peripheral blood in such scant numbers as to be overlooked. In the hypoplastic and hemolytic anemias, bone marrow studies permit quantitative estimation of the cell types involved in the disorder. Bone marrow examination serves as a guide to therapy with anti-anemia agents by permitting observation of their effects upon maturation of the earlier red cell forms. The indications for the administration of folic acid, for instance, in the syndrome of megaloblastic anemia of infancy which recently was described¹ are better controlled with the aid of bone marrow studies.

The need for careful study of alterations in the white cells has increased since the advent of drugs known to produce agranulocytosis such as the sulfonamides and thiouracil. The effect upon hematopoietic organs and the possible value of therapy in restoring the white cells to normal levels are more accurately determined by study of the parent cells in the sites of origin. In addition to direct inspection of the precursors of the red and white cells, the examination of the bone marrow permits a study of platelet formation. In intrinsic hemorrhagic disorders it permits not only an estimate of the reaction of bone marrow to the loss of blood but direct observation of megakaryocytic con-

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rinsing with any bland alkaline mouth wash is indicated. Continuous warm wet dressings are valuable for vesicobullous types of erythema multiforme, boric acid (2 per cent), Burow's solution (1:30) or potassium permanganate (1:10,000 to 1:3,000) are suitable. Prolonged starch baths may be most comforting if the patient is afebrile, oatmeal or bran baths and weak potassium permanganate baths may be equally good. In the drying phase of this exudative eruption, boric acid or zinc oxide ointment and Lassar's paste are useful.

Prevention.—Erythema multiforme is frequently of recurrent nature and a search for etiologic agents is of primary importance between attacks, to prevent its return if possible. Chronic systemic disease and focal infection should be sought and eliminated. Rheumatic fever may occasionally manifest itself in a multiform type of eruption. Tuberculosis can behave similarly but is less often seen to do so in America than in Europe. Food or drugs which may be under suspicion can be identified only by the administration of small doses and observing the effects. There are some apparently idiopathic cases that erupt each spring and fall without apparent reason and no cause can be demonstrated.

IMPETIGO

Impetigo is extremely contagious and good treatment depends upon three principles. The first principle is the cleaning up of all lesions, i.e., cleaning off the tops of vesicles or bullae, the crusts which may be adherent and any peripheral dead skin. This is a most important feature regardless of any later treatment. This may be accomplished by soap and water, 0.5 to 1.0 per cent liquor cresolis compositus or Lysol, equal parts of peroxide and oil, or saturated boric acid solution.

Local Therapy.—The second principle is the application of the chosen antiseptic agent, either ointment or liquid, as the case may be. Penicillin ointment, at eight to twelve hour intervals, is very effective, 500 to 1000 units per cc. in aquaphor does very well. If there is any evidence of sensitization such as redness or itching following treatment, this should be discontinued.

Sulfonamide preparations have caused so many cases of sensitization that it is inadvisable to use them.

Ammoniated mercury, 2 to 5 per cent in boric ointment, is effective in children. For older individuals the following ointment is often better: salicylic acid and precipitated sulfur, of each 6 per cent in white vaseline.

Prevention.—The third principle consists of advising the individual or family with regard to proper preventive measures. The individual should be isolated to the extent of keeping from actual contact with other individuals, directly or indirectly. Hands should be washed carefully after dressings. Contaminated toys, wearing apparel and the

like should receive due attention. The fingers and hands should be kept away from lesions, and the dressings destroyed, preferably by burning.

PITYRIASIS ROSEA

Systemic Therapy.—Although accepted as a disease entity, pityriasis rosea is of unknown cause. Systemic treatment is seldom required, save in the exceptional patient who has mild malaise or gastrointestinal symptoms, when soporifics may be justifiable. The disease is self-limited and usually runs its course in about eight weeks but may last much longer if unrestricted. A foreign protein injection (one-tenth dose of typhoid vaccine) may have an abortive effect if given in the first few days of the eruption. No other systemic therapy is of appreciable use.

Local Therapy.—Erythema or suberythema doses of ultraviolet light each two or three days constitutes the most effective treatment. If pruritus is annoying, the variants of calamine lotion are most useful, the addition of menthol 0.1 to 0.25 per cent, phenol 0.5 to 1.0 per cent, solution of coal tar 3 to 5 per cent or aqua hamamelis 10 to 20 per cent is suitable. Starch, bran or oatmeal baths may be most soothing. In drying and scaly stages boric acid ointment or 3 per cent salicylic acid cream afford much comfort.

Prevention.—No means of avoiding pityriasis rosea is known. One attack nearly always provides immunity.

PSORIASIS

Systemic Therapy.—Although one of the best known and earliest identified of diseases of the skin, psoriasis remains an etiologic enigma. Almost the only logical approach on the basis of causal therapy is a reduction of fat consumption, since there is a possible disturbance of lipid metabolism in this condition. The use of lecithin derivatives, lipocaine and sarsaparilla extract have been claimed to aid fat metabolism but their use in psoriasis has been generally disappointing. Some patients are said to do better with restriction of protein or carbohydrate intake. Vitamin treatment was tried at great length without noteworthy effect in most instances, some cases improve with vitamin D, others with thiamine, and a few on vitamins A and C taken together. The time-honored Fowler's solution has been largely discredited because of late keratotic and epitheliomatous sequelae, except in the aged. Sodium cacodylate injections, autohemotherapy and foreign protein injections may occasionally be utilized with benefit. Attempts at endocrine treatment seem useless. Psoriasis is found predominantly in otherwise healthy individuals and treatment from the general medical standpoint is usually not indicated. Adequate rest and freedom from worry are desirable.

It is worthy of note that psoriasis has not infrequently been observed to exacerbate severely when sulfonamide medication is employed for intercurrent episodes, and an occasional case will even develop the eruption for the first time during or after sulfonamide administration

Local Therapy.—Perhaps no other skin disease requires more versatile topical treatment than psoriasis, it must vary with the stage of the disease, the areas affected, the sensitiveness of each skin, the preceding treatment and what one might call “the mood of the skin” at the moment. Repeated changes are often necessary as one remedy or another becomes temporarily ineffective or not tolerated, perhaps only to prove beneficial again at some later date. Caution must be exercised to use mild measures when the disease is acute or spreading, since overtreatment can easily lead to exfoliative dermatitis at such times

Ultraviolet light therapy, preferably by sun exposure, is the easiest and least annoying form of local treatment, there is but a small percentage of patients who become worse with it. Reasonable care is desirable since a burn may be harmful. Combining the photosensitizing effect of tar with ultraviolet light is often the most effective of all measures, a 5 to 10 per cent coal tar ointment is applied at night, the residue is removed with oil in the morning, and a suberythema dose of light administered. Most people object strongly to the use of any of the tars because of the odor and staining quality, solution of coal tar may be painted on and followed immediately by ultraviolet light exposure with much less complaint from the patient. All ointments are an inconvenience from the standpoint of discomfort, time required for application, soiling of linen, and frequently required assistance in their use. Nevertheless they are nearly always necessary in the treatment of psoriasis. Benefit can usually be obtained from ointments containing sulfur, salicylic acid, ammoniated mercury, coal tar, birch tar, juniper tar, or resorcin, all are used singly or in various combinations at strengths of from 3 to 12 per cent. They can occasionally be employed in greaseless bases, alcoholic solutions and chloroform or collodion paints with good effect and are less objectionable to use. Ointments of dioxyanthranol (0.1 to 0.5 per cent) or chrysarobin (0.5 to 10.0 per cent) may be applied to restricted areas in stubborn cases but can give rise to intense irritation and must never be used on or near the face.

A warning should be observed in regard to x-ray therapy in psoriasis. This modality has been employed with success but its benefit is transient. The desire for continued relief leads patients to seek more radiation from other physicians when one declines to give it again. It is impossible to determine accurately the previously treated areas and radiation sequelae with possible future epitheliomatous degen-

eration will result. Many dermatologists do not countenance the use of roentgen radiation in this disease.

It cannot be overemphasized that mild conservative measures must be employed in the acute phases of psoriasis. An acute case should be managed with soothing baths, weak wet dressings and the mildest of lotions and creams. Often only starch baths and petrolatum or boric ointment will be tolerated. In these instances the skin behaves as in any acute inflammatory eczematoid dermatitis, the condition is analogous to a burn.

The scalp requires special attention and is harder to handle since ointments are more difficult to use in the hair. Ointment bases of the emulsion type may be prescribed as "water-soluble base" and will wash out more readily. Tar creams should be used in only 3 to 5 per cent strength in the scalp. An ointment of salicylic acid (3 to 6 per cent) and ammoniated mercury (6 to 12 per cent) is often very effective. Chrysarolin must be strictly avoided in the scalp, severe dermatitis of the eyelids and face nearly always follows its use. Mild psoriasis of the scalp can often be controlled with alcohol lotions containing salicylic acid, resorcin, solution of coal tar or resorcinol monoacetate. Sulfated oil detergents, tar soaps or tincture of green soap are suitable for shampoos. Psoriasis of the face must always be treated more gently than most other areas.

Prevention.—If a dietary regimen is found of value in any given case of psoriasis, the continuance of that regimen while in a state of remission should help prevent or at least postpone recurrence of the disease. Not much else can be offered. It is possible that prophylactic topical therapy to certain favorite sites during clear periods may help and keep them free.

SCABIES

The detection of scabies in a cleanly individual is difficult and persons with suspicious lesions should probably be isolated until a definite diagnosis can be made. The uncomplicated cases respond very well to the so-called twenty-four hour treatment with Danish ointment, and also with benzyl benzoate preparations. The latter has been used frequently in recent years and has an excellent record. It is usually prescribed as an emulsion and either painted on or sprayed over the body surface. A 30 per cent emulsion is the most frequently used following a cleansing bath. Danish ointment, a rather complex formula, containing sulfur, potassium and sodium hydroxide, zinc sulfate, in a base of petrolatum, wool fat and liquid petrolatum has accomplished extremely favorable results. Instructions for its use should be rigidly followed. After a thorough cleansing bath the ointment is applied to body from chin to soles of feet. The patient should put on his pajamas after ten to fifteen minutes and remain in those clothes

for twenty-four hours. Another cleansing bath is taken and clean clothing donned. Bed and body clothing should be adequately sterilized. In general Danish ointment produces less irritation and the record of cures with one application is very high.

Prevention.—Prevention of scabies lies in the early diagnosis and prompt treatment. Meticulous attention to the details of treatment is essential. Careful sterilization of clothing is important. A high index of suspicion is desirable. In order to prevent later complications of treatment advice should be given with regard to starch baths and the use of calamine lotion following the cleaning up after using the ointment.

SEBORRHEIC DERMATITIS

Systemic Therapy.—There is an alteration of the function of the sebaceous glands in some individuals that leads to a so-called "seborrheic diathesis." This state is not properly understood but we know there is hyperactivity of the sebaceous apparatus, that it is sensitive to many stimuli and easily touched off into an inflammatory eruption which may appear in widespread and distressing fashion. The constitutional background obviously cannot be changed. It may be first manifested at adolescence but endocrine therapy is fruitless. Infectious factors have not proved important but secondary infection may be quite a problem. An environmental influence may affect some cases. Dietary approach gives inconstant results, some patients do better with a low fat intake and others may benefit more from a restriction of carbohydrates. Large amounts of the B complex seem to help an occasional case, as do also injections of crude liver extract. No systemic approach seems to be of outstanding value.

Local Therapy.—As in the treatment of psoriasis, the wide variety of agents employed in treating seborrheic dermatitis provides evidence that an eminently satisfactory approach is still to be found. In different stages of the disease and in accordance with the areas affected, topical applications may include such agents as sulfur, mercury, salicylic acid, resorcin, resorcinol monoacetate, ichthyol, and of the tars, cinnabar, pyrogalllic acid, anthralin, chrysarobin, silver nitrate, gentian violet or malachite green, these are often employed in various combinations. It should be stressed that the scalp is somewhat of a master key to the problem and should receive diligent attention, no matter how mildly it may seem to be affected. Lotions often suffice if activity is slight, mixtures of mercuric bichloride, resorcinol monoacetate and spirits of formic acid, or containing phenol and salicylic acid are frequently efficacious. Solution of coal tar may be added to the latter. Sulfur, sulfur and salicylic acid, ammoniated mercury and salicylic acid, resorcin or tar creams are commonly employed in more stubborn scalps. Water-soluble emulsion bases are most desirable for these

preparations Chrysarobin should never be applied above the shoulders. Sulfated oil detergents, tar soaps, sulfur soaps or tincture of green soap are useful for shampoos. When the face is affected, scalp ointments should be used half strength. Sternal or interseapular involvement may require stronger percentages of active ingredients than the scalp, or a change to some of the agents previously listed.

When seborrheic dermatitis spreads to the flexural areas, such as axillae, submammary and umbilical regions, or genitocrural, inguinal and intergluteal areas, it often does so with almost explosive speed and becomes an acute inflammatory disease. These are many times sufficiently severe to demand bed rest or hospitalization and the most bland of topical measures are imperative, just as in acute psoriasis. Soothing baths and boric acid ointment, mild wet dressings and the simplest lotions are indicated. As the inflammation subsides, weak wet dressings with silver nitrate (0.1 to 0.25 per cent) or resorcin (1 to 2 per cent) may be tolerated. A bland cream of value may be made up with Burow's solution 1 part, anhydrous lanolin 2 parts, and Lassar's paste 3 parts. In the subacute phase the dyes are often of great value, these include 1 per cent malachite green, 1 to 2 per cent gentian violet, or 1 per cent acriflavine, all in aqueous solution and applied as paints. Silver nitrate may be used similarly in 2 to 10 per cent strength. Calamine lotion or liniment with the addition of sulfur, ichthyol, solution of coal tar or resorcin, is a later step. A paste of 40 per cent sulfur in petrolatum, gently applied, is frequently useful. The ointments used for ordinary seborrheic dermatitis are seldom necessary in this intertriginous type of the disease and probably would not be well tolerated at any time. In the axillary and pubic regions where hair is profuse, it is frequently advisable to avoid the use of ointments altogether.

Prevention.—Little can be done in basic prevention of seborrheic dermatitis but adherence to a beneficial dietary regimen, strict attention to scalp hygiene and avoidance of irritation in areas of predilection are advisable. Continuation of therapy for some time after apparent cure may be of value.

TINEA CAPITIS

Present epidemics of ringworm of the scalp emphasize the need for early diagnosis and careful treatment. The diagnosis should be confirmed by microscopic or cultural examination or at least by the use of a Woods filter. The latter is a filter of nickel oxide glass used with an ultraviolet light in a darkened room. The infected hairs show up as fluorescent filaments.

Local Therapy.—In those cases caused by the *Microsporon audouinii*, epilation by x-ray provides the quickest cure. Three hundred roentgens of unfiltered x-ray to each of five areas of the scalp should pro-

duce epilation with a resultant cure. Such x-ray treatment should be given only with an accurately standardized apparatus and technic, and under the direction of a physician experienced in the use of this method. No local antiparasitic treatment should be used until approximately two weeks after treatment. An antiseptic ointment such as the following should be used to prevent recurrence: phenol 6 per cent, betanaphthol 6 per cent and precipitated sulfur 12 per cent, in petrolatum alba. This ointment and manual epilation can be used in children too young to be treated with x-ray. In the treatment of other types of ringworm of the scalp the fatty acid preparations are being used more extensively. Under this heading are Desenex ointment and Sopronol ointment and liquid. The former has been used a little more extensively. Manual epilation of infected hairs is necessary. Even with this procedure the treatment is still protracted.

Prevention.—Prevention consists in ascertaining if an infected animal was the cause, and if so, either of treating or disposing of the affected animal. Children with active lesions should preferably remain at home from school and should avoid physical contact with other individuals. A stocking cap changed and sterilized daily is valuable. Frequent washing of the scalp and care of the hands are very necessary.

DERMATOMYOSITIS ASSOCIATED WITH METASTASIZING BRONCHOGENIC CARCINOMA

A Clinicopathological Conference

ROBERT P. MCCOMBS, M.D., F.A.C.P.* AND
H. EDWARD MACMAHON, M.D., M.R.C.P. (London)†

DR. MCCOMBS In most clinicopathological conferences, the custom long has been to present a case history to a reviewer who is unfamiliar with the patient or with the pathological findings and who then by logical deduction or by astute guesswork may arrive at something approximating the proper diagnosis. In such a presentation, the reviewer has certain advantages over the clinicians who saw the patient, because all findings have been briefly summarized, presumably including all of the pertinent information and excluding much of the irrelevant information that often besets the clinician. In postmortem cases, he has the advantage of knowing that the patient had a fatal illness and, more than likely, one of unusual interest, whereas the clinician may be sure of neither of these facts during the patient's life. If the reviewer fails to reach a proper diagnosis, much of the pedagogic value of the case history is lost.

In the case to be presented, no diagnosis was reached before death occurred, and the postmortem findings were very unusual. It seems unfair, therefore, to ask a reviewer to discuss this case as an "unknown." Yet certain questions worthy of discussion are raised by the findings.

We shall present the clinical history and pathological findings and conduct the discussion at their conclusion.

CASE REPORT

Medical History.—R. H. (No. 19-557), a white male insurance broker, 55 years of age, was admitted to the Joseph H. Pratt Diagnostic Hospital on August 17, 1946.

Chief Complaint.—Weakness, rash.

Present Illness.—This patient was perfectly well except for a long-standing mild 'cigarette cough' and a mild chronic backache until February or March 1946, when he began to notice moderate general fatigue which he attributed to overwork. At about the same time he developed an intermittent vague pain in

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the upper abdomen. This was not related to meals but seemed to develop after prolonged sitting. He also noted that when this pain was present his right upper abdomen was tender to pressure.

On July 4, 1946 he experienced a mild general sunburn. Two weeks later he was again exposed to the sun. Following this he developed an unusual skin reaction consisting of a diffuse raspberry shading on the face, neck and arms, with superimposed darker spots. This itched intensely and scaled instead of peeling. Associated with the rash the pre-existing fatigue became much more noticeable so that he was unable to climb stairs or to perform sustained activity. Shortly thereafter he noted fever and sore throat. He was put to bed and given oral sulfadiazine and, later, oral penicillin.

On August 3, 1946 he was admitted to the Lawrence Memorial Hospital in Medford, Massachusetts, where intramuscular penicillin was given, with no relief. Instead, marked swelling of the eyes, nose and mouth developed and the inside of the mouth became sore. Penicillin was discontinued. Intermittent fever to 102° F continued and weakness of the legs was pronounced. Lower abdominal pain and abdominal distention developed. Hemoglobin determination and red and white blood counts were normal. Agglutination tests for typhoid and undulant fever were reported as being negative. X-ray examination of the chest on August 5 showed that the lung fields were clear except for "increased markings due to bronchitis." The heart appeared to be normal. A flat film of the abdomen on the same date showed nothing unusual other than hypertrophic arthritis of the lumbar spine and pelvis. A barium enema done on August 14 was normal. Prostagmine bromide (1 cc.) was given for the abdominal distention, and considerable temporary relief of this symptom resulted. Because of failure to improve and the lack of a positive diagnosis, the patient was referred to this hospital.

Family History—Mother and maternal grandmother died of cancer. Father died of tuberculosis. One sister died of an unknown cause at the age of 48 years.

Past History—The history was negative except for measles in childhood. The patient had always lived near Boston. There was no history of major or minor allergies.

System Review—No information of significance was obtained.

Physical Examination—Temperature 100.2° F, pulse 106, respiration 21. The patient was well developed and well nourished but appeared to be quite sick. He was alert and cooperative. His face was edematous and his eyelids were almost closed. The skin over the face, neck, upper thorax, lower arms (particularly on the elbows and hands), on the lower portions of the legs and in the perianal region showed a striking, diffuse, deep red macular rash with scaling. In certain areas, particularly on the fingers and around the fingernails, there were dark purpuric spots. The head was normal. The optic fundi appeared to be normal and the pupils reacted normally. There was a slight convergent squint. The nose and ears were not remarkable. The interior of the mouth was markedly injected and the mucous membrane of the posterior part of the palate was partially denuded. The tongue and gums were red and somewhat swollen. All teeth had been removed. The trachea was in the midline. The thyroid gland was questionably enlarged. Both sides of the chest expanded equally and percussion and breath sounds were normal. Coarse rales were heard but these cleared on coughing. The heart seemed normal. The blood pressure was 120/85. The abdomen was tense, distended and difficult to examine. There were tenderness on the right side and questionable spasm. The liver, spleen and kidneys could not be palpated. Deep palpation in midabdomen was marked by tenderness. The genitalia were normal. Rectal examination was negative. No clubbing of fingers or toes was noted. The biceps, triceps, patellar, radial, Achilles and plantar reflexes were normal. The vibratory sense was intact. Straight-leg raising was definitely limited bilaterally because of soreness of the

muscles of the legs. The neck was not stiff. In the left calf there was an area of tenderness to deep pressure.

Laboratory Studies.—Hemoglobin 11.9 gm., red blood count 4,280,000, white blood count 10,000, polymorphonuclears 85 (23 band forms), lymphocytes 10, monocytes 2, metamyelocytes 3. Smear showed one nucleated red blood cell and slight-to-moderate variation in size and shape of the cells. Platelets were normal. Blood sedimentation rate (Westergren) 10 mm in 20 min., 55 mm in 1 hour. Nonprotein nitrogen 30 mg per 100 cc. Wasserman, Hinton and Kahn tests negative. Stool examination normal. Blood culture no growth. Prothrombin time 13 seconds (control, 14 seconds). Urine specific gravity, 1.021, albumin 0 to 1 plus, rare white blood cells, no casts, urine bilirubin and porphyrins negative.

Electrocardiogram.—Normal sinus rhythm, PR and QRS intervals normal, T₁ low. Diagnosis "Myocardial damage(?)".

Clinical Course.—Intermittent fever, with temperatures of 99° to 102.6° F continued. On August 19 during the early morning, the patient complained of abdominal and leg pain and became temporarily disoriented but responded promptly. Lesions on elbows broke down. He suddenly became worse on August 21, early in the morning, and had rapid respirations, with signs in the chest of bronchopneumonia. A bedside chest x-ray examination showed "left lower lobe, bronchopneumonia." His temperature rose to 104.6° F and he expired at 1 P.M. on August 21, 1946.

Final Clinical Diagnosis.—Undiagnosed disease (? lupus erythematosus disseminata) with terminal bronchopneumonia.

DR MCCOMBS: Are there any questions or suggestions?

QUESTION: How much sulfonamide did he receive?

DR MCCOMBS: One gram every four hours for three days.

QUESTION: Were there any complaints referable to the joints?

DR MCCOMBS: None at all.

QUESTION: Was there any past history of sensitivity to the sun in a previous year?

DR MCCOMBS: No.

QUESTION: Was a biopsy taken?

DR MCCOMBS: No. We were considering the diagnosis of lupus erythematosus, but our experience with biopsies in making this diagnosis has not been very satisfactory and so it was not done in this case. Dr. MacMahon will now give us his findings.

PATHOLOGICAL FINDINGS

DR MACMAHON: The autopsy findings were of great interest because they were unusual, involved every system in the body, and were definitely thought-provoking.

Gross Findings.—The body was that of a well-developed and moderately well-nourished white male, of about 55 years of age. The body weight was 110 pounds. The skin was very pale and areas of the body were marked with a granular scaly hemorrhagic and somewhat macular rash. This involved the forehead and scalp, the eyelids and cheeks, the interscapular area and fingers and, to a lesser extent, the axillary and anterior surfaces of the chest. There was a small solitary decubitus ulcer over the sacrum and there was a small area of fresh hemorrhage into the skin about the anus.

tent and the extent of platelet formation. In blood dyscrasias accompanied by anemia, leukopenia and thrombocytopenia, a more accurate diagnosis is, therefore, possible from study of the marrow. Smears from sternal puncture may also reveal diagnostic cells in disorders of abnormal lipid metabolism such as Gaucher's and Niemann-Pick's disease and occasionally of metastatic malignant growths.

The purpose of this presentation is to consider the alterations occurring in the bone marrow in the more common blood dyscrasias of infants and children. This review, based on the experience of the writer, agrees in its major pathologic features with those of like conditions recorded by other observers. Discrepancies in reported values for normal subjects and in those with blood disorders can be traced to differences in procedure and in the identification of the cellular components of the bone marrow. Notwithstanding these shortcomings it has been possible with simplified methods of obtaining the specimen and preparation and staining of the smears to arrive at values which serve as diagnostic guides.

TECHNIC OF STERNAL PUNCTURE

A satisfactory puncture site for bone marrow aspiration is located in the midline over the body of the sternum at the level between the second and third ribs. In infants in the neonatal period the needle is inserted at the midline into the manubrium. After preliminary disinfection, the skin and subcutaneous tissues over the site to be punctured are infiltrated to the periosteal layer with 1 per cent procaine solution. While the procaine takes effect, a dry 10 cc. syringe is rinsed with 5 per cent sodium citrate solution and the excess is expelled so that only a thin layer of the anticoagulant adheres to the inside of the barrel and syringe. This is important in children where through lack of cooperation and the restricted area for puncture several attempts may be required to withdraw the sample. A shortened spinal puncture needle is employed which is adapted to the age of the child. A 20-gauge, $\frac{1}{4}$ inch length is used for very young infants, 19-gauge, $\frac{1}{2}$ inch for older infants and young children, and 18-gauge, $\frac{3}{4}$ inch or 1 inch for older children.

The needle is inserted until it is firmly lodged without support within the interior of the sternum. The "give sensation" felt when needle enters the medullary cavity of an adult is not usually experienced in young children and occasionally one has to depend on more than one attempt at aspiration before the proper depth is reached. The stylet is removed and the syringe is securely fixed to the needle to obtain maximum suction. To minimize admixture with circulating blood only 0.1 to 0.2 cc. of marrow contents are withdrawn. The aspirated fluid is expelled on a slide from which a count of total nucleated cells of the red and white cell series is made with 2 per cent acetic acid.

The chest and abdominal muscles were particularly well developed. The pectoral muscles were firm, dark red, glistening and homogeneous. In contrast, the abdominal muscles were mottled light red, pink and grayish yellow. These discolored patches varied in shape and in size. They were rather sharply demarcated and were swollen and more tense than the healthy dark red muscles of the chest. A similar patchy discoloration was seen in the third right intercostal muscle, in both sternocleidomastoids, and in the omohyoids and sternohyoids. No attempt was made to examine all muscles of the body but in the shoulder area there was found a large solitary yellowish-gray patch in the upper portion of the left deltoid. Many incisions made into the thighs revealed only healthy dark red muscle. The skin and subcutaneous tissues adjacent to the involved muscles in the cervical region were edematous.

The peritoneal cavity was empty and entirely free of the hemorrhagic lesions seen in the skin. The original midline incision encountered a solitary marble-sized tumor nodule projecting into the peritoneal cavity at a point midway between the umbilicus and pubis. This nodule was firm, homogeneous, glistening and gray. The liver was large and extended a whole handsbreadth below the xiphoid and 4 finger-breadths below the right costal margin. Its surface was covered with grayish-white umbilicated tumor metastases, varying from 1.5 to 2.0 cm in diameter, and its lower inferior margin was deformed and nodular. A number of large marble- to prune-sized nodules of tumor tissue were visible in the gastrohepatic ligament, and along the upper border of the pancreas. A similar cluster of large lymph nodes was palpable in the celiac area and at the base of the mesentery of the small intestine. The only other significant findings in or about the peritoneal cavity were a few fibrous adhesions between the gallbladder and the duodenum and between the sigmoid and the left lateral pelvic wall.

Both pleural cavities were completely filled by large distended lungs, whose anterior margins touched in the superior mediastinum. There were a few old string adhesions along the medial surfaces of both pleural cavities binding the lungs to the pericardium. On the left side a small patch of fresh fibrin covered the most dependent portion of the lower lobe. There were 10 cc of blood-tinged watery fluid in the left pleural cavity.

Organs of the Chest—A small thymic fat pad contained several large firm lymph nodes. The heart was small (weight 260 gm). The pathological findings in the heart may be summarized as follows. There was slight hypertrophy and dilatation of the right ventricle, the left ventricle was moderately firm, well contracted, and empty, there was a small area of thickening along the anterior aortic leaflet of the mitral valve, to which were attached two thickened chordae tendineae, brown pigmentation and atrophy of the myocardium, patchy fibrosis of the pericardium and a minimal deposition of lipid in both coronary arteries also were noted. In examining the pulmonary artery and its two main branches in situ, it was possible to pass the index finger far into the right pulmonary artery, on the left side, this was not possible because there was a ringlike constriction of the left pulmonary artery in the hilar area.

The respiratory tract was carefully examined in situ. The vocal cords were edematous and the inner surface of the larynx and upper two-thirds of the trachea were coated with pus. The lower third was completely filled with an odorless, thick, yellow, sticky, purulent exudate that formed a cast which could be raised and lowered by alternately compressing and releasing either lung. The right bronchial tree could readily be traced to the periphery of the lung, all branches contained a purulent fluid exudate. An examination of the left bronchial tree revealed a distinct narrowing of the lumen at the point of bifurcation of the primary bronchi. Here, the wall was encroached upon from without by a nodular hard solid mass of gray-white tumor tissue. Beyond this constricting ring, the lumina were distended with

pus At a point 3 cm from the origin of the bronchus to the left upper lobe, the normal mucosa was interrupted for a distance of 2 cm by a well defined encircling tumor 2.5 cm in diameter. The lumen in this zone was reduced to about one-quarter of its original size. The tumor extended peripherally into the surrounding lung tissue. Metastases replaced much of the regional lymphoid tissue, and tumor tissue was clearly visible in the tracheobronchial nodes and in the lymph nodes of the posterior mediastinum. The left innominate vein was encircled and compressed by tumor but the lumen itself was neither completely occluded nor penetrated. The sympathetic chain of nerves, the adjacent pleura, the aorta, thoracic duct and esophagus were free. In addition to the inflammatory exudate in the bronchi, both lungs showed small patches of inflammatory consolidation in the lower lobes, particularly on the left side.



Fig 168—Section from the primary tumor of the bronchus. The surface epithelium is no longer present. A somewhat granular basement membrane acts as a limiting membrane between the lumen of the bronchus and the tumor. The normal architecture of the wall is almost entirely replaced by a sea of tumor tissue. Diagnosis "Oat-cell" carcinoma of the bronchus.

In the neck, many of the lymph nodes on each side were swollen and edematous. The thyroid gland was small, firm, light brown and regular in outline.

Organs of the Abdomen—The spleen was larger than normal (weight 265 gm). It was firm and dark red, and homogeneous on section. In examining the extrahepatic biliary system, a little light-orange watery bile could be expressed from the common duct, and a darker green but equally watery bile was expressed from a small, partially collapsed gallbladder. The liver was large (weight 2210 gm). Much of this increase in size and weight was due to metastatic tumor tissue. As many as forty metastatic nodules could be counted in any of the transverse sections. An interesting feature of these metastases was their uniform distribution and their similarity in respect to size. Each was about 2 cm in width. The intervening liver parenchyma was congested and edematous. The adrenal glands were enlarged and partially replaced by metastatic tumor tissue. Each kidney was uniformly flecked

with minute gray-white nodules measuring 0.1 to 0.3 cm in width. The prostate gland, grossly, was normal. The aorta showed a moderate degree of arteriosclerosis. The abdominal and thoracic vertebrae showed no gross deformity but they could be cut most easily. The marrow was mottled red and gray. The psoas muscles were dark red and could readily be teased apart.

The Head—The calvarium was unusually thin. The leptomeninges were edematous and opaque, especially over the frontal and parietal areas. The brain (weight 1395 gm) was large, swollen and sticky. The subcortical white matter of both hemispheres was riddled with minute gray and red metastases. These were remarkably similar and, like the metastases in the kidneys, varied from 0.1 cm to 0.3 cm in width.

Gross Diagnosis—*Primary carcinoma of the bronchus with metastases*

Dermatomyositis, healed endocarditis, healed pericarditis, chronic or healed sclerosing leptomeningitis



Fig. 189—Section from the prostate. This field was selected to show an area of metastatic tumor tissue replacing normal prostate. Diagnosis: *Metastatic carcinoma, "oat-cell" type, from a primary tumor of the bronchus*

Purulent tracheitis, bronchitis, and bronchopneumonia, terminal cerebral edema

Histology—There was a rapidly growing "oat-cell" carcinoma of the bronchus (Fig. 188). It had invaded lymphatics and veins. Metastases were found in all adjacent lymph nodes, and distally, in abdominal and retroperitoneal nodes, in the liver, adrenals, kidneys, in the bone marrow of the ribs and vertebrae, in the brain, peritoneum and prostate gland (Fig. 189).

Many sections were taken from involved areas of the skin and all showed an inflammatory reaction centered about the small vessels in the upper layer of the edematous corium. The epidermis was coated with many layers of swollen, cornified cells and precipitated protein (Fig. 190). There was no stratum granulosum. All vessels were dilated and many were surrounded by histiocytes, lymphocytes and an occasional plasma cell and eosinophil. The basement membranes of an occasional arteriole and scattered collagen bundles were swollen and overstained with eosin.



Fig 190—Section of skin showing a scaly retention of the surface epithelium. The corium is edematous. Arterioles, venules and lymphatics are dilated. There is a moderate pervascular infiltration of inflammatory cell. Diagnosis: *Acute dermatitis*.

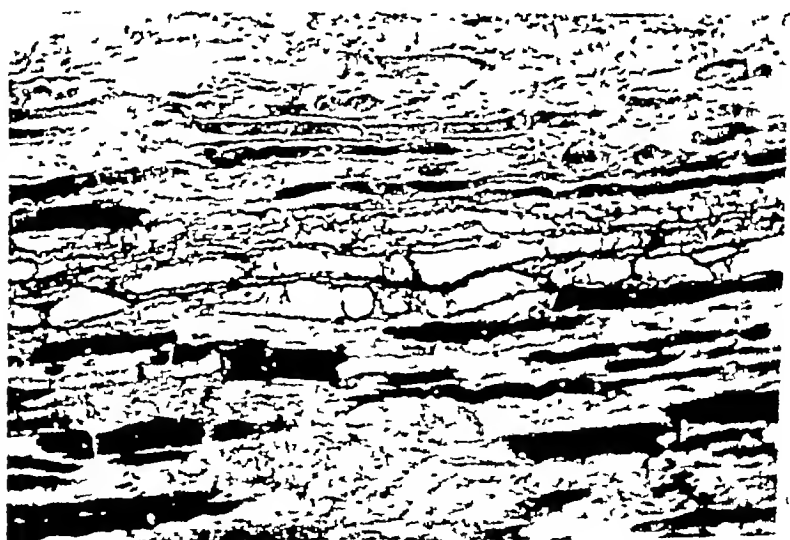


Fig 191—Fragmented and necrotic muscle fibers that have lost all striations. The interstitial tissue is soaked in an acute acellular serous inflammatory exudate. Diagnosis: *Acute necrotizing myositis*.

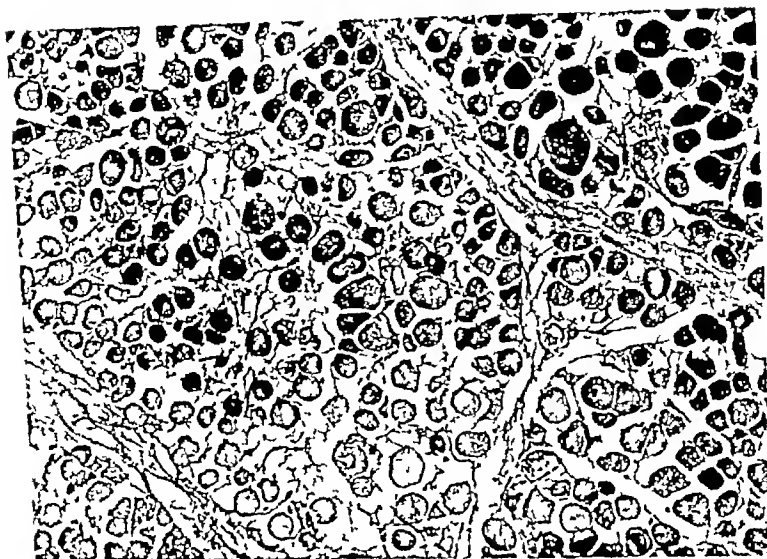


Fig 192—Muscle fibers in cross section All fibers are necrotic, swollen, overstained and free of nuclei The intercellular tissue is bathed in an inflammatory serous exudate Diagnosis *Acute myositis*

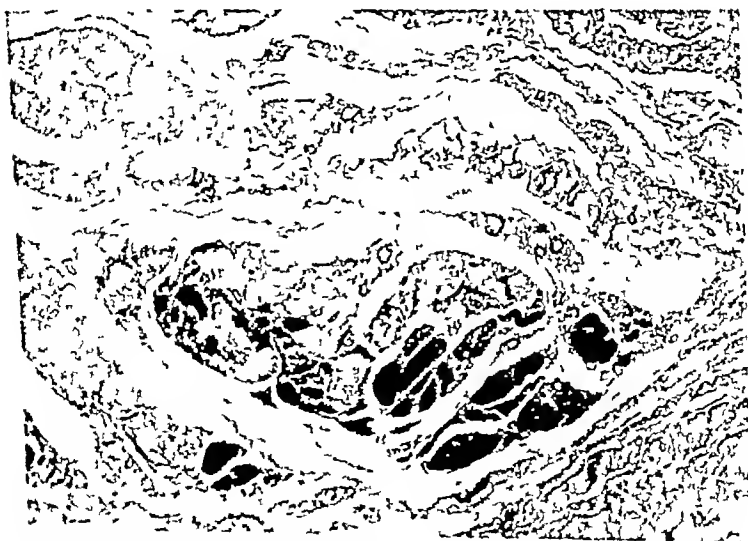


Fig. 193—A few viable muscle fibers are embedded in condensed collagen These are the only viable muscle fibers in what was once a solid homogeneous mass of muscle tissue Diagnosis *Healed myositis with scarring*



Fig. 194—Lying in the midst of skeletal muscle fibers is a medium-sized vein. The lumen is dilated, the lining cells are absent, the wall is soaked with red blood cells and fibrin and there is a minimal proliferation of cells about the adventitia. Diagnosis: *Acute phlebitis*.



Fig. 195—Section from the leptomeninges showing an area of sclerosing edema. There are a few fibroblasts embedded in a loose collagenous ground substance. Diagnosis: *Sclerosing edema of the meninges*.

The skeletal muscles were of particular interest. Some showed very little change, others, although appearing normal grossly, revealed isolated necrotic muscle fibers. Others that were obviously mottled and swollen, showed swelling, vacuolation, coagulation necrosis, and fragmentation of every fiber (Fig 191). The intercellular tissue was the seat of an intense serofibrinous inflammatory edema (Fig 192). Many of the small arteries and veins showed an acute inflammatory reaction and saturation of their walls with fibrin and red blood cells. There was very little cellular exudate. In the most acute lesions, inflammatory cells were entirely lacking. In some areas where muscle fibers had disappeared, there was little condensation of collagen (Fig 193).

The blood vessels in different parts of the body, quite apart from the skin and muscles, were involved in an inflammatory reaction—sometimes acute, sometimes chronic, and sometimes healed. As far as could be seen, it was the smaller muscular arteries and veins that had suffered the brunt of the reaction (Fig 194). The acute lesions were characterized by necrosis of the vessel wall. The chronic lesions showed a sclerosing edema of all three layers. The healed lesions manifested themselves by intimal and adventitial scarring.

On the surface of the pericardium, and in the endocardium in the region of the mitral valve, there was considerable fibrosis. The leptomeninges were thickened by a loose edematous increase of collagen (Fig 195). Sections through the cortex of the brain, remote from metastases, showed patchy demyelination. In the respiratory tract, acute laryngitis, tracheitis, bronchitis, and bronchopneumonia were accompanied by acute inflammation in the regional lymph nodes.

FINAL DIAGNOSIS

This combination of dermatitis and myositis warrants establishing the diagnosis of *dermatomyositis*. The disseminated angitis, the healed endocarditis and pericarditis, as well as the sclerosing meningitis, appeared to belong to the same syndrome. The patchy subcortical demyelination was of interest because a similar lesion has recently been found at autopsy in a fatal case of scleroderma. The inflammatory reaction in the muscles was most striking. There were acute lesions, healing lesions, and others that were completely healed. From a study of many sections it seemed that this acute inflammatory reaction in the muscles was but a terminal episode in a much older and possibly recurrent disease. The changes in the vessels occurred in arteries, veins and capillaries. The lesions were widely scattered and resembled those seen in disseminated angitis as seen in lupus erythematosus. The changes in the meninges and pericardium were in the nature of a chronic inflammatory sclerosing edema.

The primary carcinoma of the bronchus with its widespread metastases indicated an early blood stream dissemination. There were several interesting features about these metastases. First, they had the same widespread distribution, except for their absence in the spleen, as miliary tubercles from a pulmonary focus of tuberculosis. Second, all the metastases in the brain were of about the same size. The same was true of those in the kidney and of those in the liver and in both adrenal glands, but it was noticed that the metastases in the liver and adrenal glands were all very much larger than the small uniform

metastases in the brain and kidneys. If all organs were involved simultaneously with metastases, then the rate of growth of tumor tissue in the adrenal glands and liver in this patient was very much faster than that in the kidneys and brain. A third feature of interest was the presence of metastatic foci in the prostate gland. This was a very unusual finding and the diagnostic implications are at once obvious. The last point of interest in respect to the tumor deals with metastases in the vertebrae. The marrow here was replaced by tumor tissue leaving the cancellous bone morphologically unchanged. There was no lysis of bone and there was no new bone formation.

DISCUSSION

Dr. McCOMBS: The reporting of these pathological findings makes the clinician feel quite humble indeed. Here was a patient with two widely disseminated diseases, either one of which was capable of resulting in a fatal outcome, yet neither was recognized before death occurred. We had seriously entertained the diagnosis of lupus erythematosus disseminata, but had been discouraged from establishing it positively because of the age and sex of the patient, and the absence of leukopenia, or definite splenomegaly, or evidence of renal and serous membrane involvement. A competent dermatologist assured us that the skin lesions were more characteristic of a drug eruption than of lupus erythematosus. A muscle biopsy had been contemplated, but we had no real lead as to just where such a biopsy should be taken. Dr. MacMahon has told us that normal muscle often was contiguous with degenerated muscle, and even if a biopsy had been taken, there is no assurance that a positive diagnosis of dermatomyositis could have been made before death.

With regard to the primary carcinoma of the lung with diffuse metastases, I believe an antemortem diagnosis here would have been almost impossible. In the first place, other than a chronic cough which had been present for many years, there were no symptoms that might have called attention to a lung lesion except for the terminal bronchopneumonia. A chest x-ray picture taken sixteen days before death was completely normal except for some slightly increased hilar markings usually seen in patients with chronic bronchitis. As a matter of fact the autopsy confirmed the presence of a mild and long-standing bronchiectasis. Bronchoscopy might have revealed a narrowed bronchus, but the tumor was in the upper lobe beyond reach for biopsy. A peritoneoscopy or laparotomy would have revealed the metastatic abdominal lesions, but there was no indication for the performance of either of these procedures.

Dermatomyositis is not a particularly rare disease. Several hundred cases have been reported. O'Leary and Waisman reviewed forty cases seen at the Mayo Clinic between 1926 and 1959.¹ Several excellent

descriptions of the diverse clinical aspects of the disease have appeared in the literature in recent years²⁻⁵ Very few of the reported cases, however, have run courses as acute as the one we have described We have not had a similar case in this hospital The more usual course is one that lasts several months, or years The onset is usually insidious, being marked by vague muscle pains and weakness Later, severe muscle pain develops, a rash appears, and there may be edema of the face and eyelids The rash is apt to be most pronounced on exposed surfaces and has been described as being erysipeloid, roseolar, morbilliform, urticarial, eczematous or petechial In chronic cases, scleroderma may develop in the involved portions of the skin The muscles are, as a rule, edematous or nodular, later becoming atrophic and leading to debilitating contractures The muscles of deglutition and respiration may become affected and consequently, as in this case, bronchopneumonia is a frequent terminal event Fever may or may not be evident, being more common in acute cases Laboratory studies are not very helpful, the sedimentation rate is usually increased and there may be an eosinophilia Disturbed creatine metabolism has been noted in all cases in which appropriate studies have been made, but this is a nonspecific disturbance found in many other muscle disorders

The course of the disease is quite variable Death may occur within two weeks of its onset In most instances, however, there is gradual progression over a period of several months and cases lasting three or four years are not uncommon The mortality rate in these cases is said to be about 50 per cent, but in those instances in which the disease has apparently become arrested, crippling deformities are apt to persist because of muscular contractures

The diagnosis of dermatomyositis should be obvious in long-standing cases. A biopsy taken from an involved muscle shows muscle degeneration and lymphocytic infiltration O'Leary and Waisman believe that the interstitial reaction occurs secondarily, possibly due to a tissue response to the parenchymal damage This impression would seem to be substantiated by Dr MacMahon's findings in this case of marked muscle degeneration often associated with very little or no tissue reaction

Several theories concerning the etiology of dermatomyositis have been advanced, none of which have been substantiated In some of the earlier reports a variety of bacteria supposedly recovered from the degenerated muscles at autopsy has been incriminated Careful study in more recent cases has failed to support the bacterial theory. The similarity of the clinical and pathological findings in scleroderma, dermatomyositis, disseminated lupus erythematosus, the Libman-Sacks syndrome and periarteritis (polyarteritis) nodosa has led to the supposition that they may have similar causes³ At least one of these

conditions (periarteritis nodosa) has been demonstrated to occur in hypersensitivity states.⁶ Asthma and eosinophilia may occur in association with dermatomyositis.

Acute infections of the upper respiratory tract, recent parturition, and the existence of chronic diseases may precede the onset of dermatomyositis. It is interesting to speculate upon the relationship of the rapidly growing tumor and the development of the skin and muscle changes in our case. One of the cases recorded by O'Leary and Waisman was associated with adenocarcinoma of the rectum that had metastasized to the liver. Dostrovsky and Sagher⁷ reported two cases of dermatomyositis associated with malignant tumor (breast and ovary) and refer to three similar cases reported by Bezceney (ovary [two] and breast), one by Pick (ovaries) and one by Gottron (stomach). Dostrovsky and Sagher believe that the muscle and skin changes may be due to obstruction of the smaller vessels by tumor cells. No such lesions were noted here. Becker, Kahn and Rothman,⁸ on the other hand, have postulated that dermatologic manifestations occurring during the growth of internal malignant disease may result when tumor cells reach the skin and are there destroyed, setting up a cutaneous reaction.

I wonder if the skin and muscle changes may be the result of hypersensitivity reactions in these tissues to a circulating antigen of some type. In our own case this antigen might have arisen from the tumor cells or some product of their degeneration.

DR THANNHAUSER: We had a case here in which dermatomyositis was suspected and in which a tumor of the kidney was demonstrated. This association apparently occurs more frequently than is indicated by the literature.

DR MCCOMBS: A skin and muscle biopsy taken from the patient you mention showed no evidence of dermatomyositis. He developed skin, muscle and joint changes in the terminal illness and died of a renal carcinoma. Unfortunately, he died at home and a complete autopsy was not done. In reviewing some of our records of cases of presumed diffuse collagen disease I came across that of a young physician who was thought by the clinicians to have had dermatomyositis and a tumor of the sigmoid. Autopsy done at another hospital revealed a cancer of the sigmoid and skin changes typical of scleroderma, but no muscle changes suggesting dermatomyositis. While on this subject, I would like to mention two other cases seen recently. In one, the presenting symptom was pain and swelling of several joints. Exhaustive studies were made but no evidence of malignancy was uncovered. A tentative diagnosis of rheumatoid arthritis was made. Three months later the patient returned with an obviously metastatic lymph node in the axilla. Biopsy of this node showed a transitional cell tumor and repeat x-ray films of the spine now showed

as for a peripheral white cell count. In the counting chamber, megakaryocytes and the foam cells of Nieman-Pick's disease may be visualized and enumerated. Occasionally groups of neoplastic cells may also be observed in the course of the count such as in neuroblastoma.

Smears are prepared and stained on slides or coverslips as for peripheral blood with one of the accepted methods such as Jenner-Giemsa, May-Grunwald-Giemsa or Wright's stain. By shortening the period of staining employed for blood films, Wright's stain has proved satisfactory for routine smears from marrow punctures. The stain is permitted to cover the smear for one-half to one minute and after dilution with water for two minutes. A minimum of 300 cells is required for the differential count to overcome inaccuracies resulting from the displacement of cells in preparing the smears. White counts and smears are made from the peripheral blood with each sternal aspiration. It is occasionally desirable to compare corresponding white cells from both sources for more accurate appraisal of cytologic details in deciding on the classification of obscure cells.

NORMAL BONE MARROW

Information as to the normal range for the total nucleated cell count, the differential percentages for each type of cell, the variability in different age periods and the extent of individual fluctuations is still relatively limited. Despite these restrictions certain qualitative and gross quantitative alterations can be detected which reflect the functional state of the bone marrow. The criticisms that the cellularity of the marrow is not uniform and that sternal marrow is not an index of the whole mass of hematopoietic tissue is perhaps less applicable to younger persons, in whom red marrow is more uniformly distributed throughout the skeleton.

TABLE 1

RELATIVE NUMBER OF NUCLEATED CELLS IN NORMAL BONE MARROW
(STERNAL ASPIRATION)

(Total Nucleated Cell Count, Approximately 100,000 to 150,000 per Cu. Mm.)

	Range Per Cent	Average Per Cent
Myeloblasts		
Myelocytes (including promyelocytes)	1-5	2
Nonsegmented polymorphonuclears (including metamyelocytes)	10-25	20
Segmented polymorphonuclears	15-30	20
Lymphocytes	5-30	25
Nucleated red cells (principally normoblasts)	5-25	13
Monocytes	15-30	20
Plasma cells		Occasional
Reticulum cells		Occasional
Hematogones		Occasional
Megakaryocytes		Occasional
	10 to 35 per cu mm	

metastases, but none was evident near the painful peripheral joints. The primary site has not been located. Also, we have just seen a man who developed severe bronchial asthma five years ago and was carefully examined by several competent men. Only very recently was it evident that he had bronchogenic cancer with metastases. I am merely pointing out that what are considered to be allergic reactions may develop at about the same time that a tumor starts to grow. The possible significance of this coincidence is at least intriguing.

DR LEONARD: Dr MacMahon, can you tell whether or not the tumor was present before the dermatomyositis and muscle changes developed?

DR MACMAHON: There is no doubt that most of the muscle changes represent a very acute process, possibly one of no more than a few days in duration. On the other hand, the scars present in a few of the striated muscles and also in the heart, meninges, pleura and pericardium are undoubtedly much older than the tumor. If we can assume that they were caused by an earlier episode of the same process, then it is my opinion that the collagen disease preceded the primary tumor in respect to time of origin.

DR MCCOMBS: This man had no symptoms until six months before death. Are the healed lesions older than that?

DR MACMAHON: Yes.

DR MCCOMBS: If the healed and the acute lesions are part of the same process, then we can assume that no relationship existed between the cancer and the dermatomyositis. From the clinical viewpoint, however, it is helpful to try to relate two diseases whenever possible.

DR HEFFERNAN: Was there any relationship between the location of the skin lesions and the muscle changes?

DR MACMAHON: Here and there muscle changes were noted underneath an area of dermatitis, but most of the muscle damage occurred beneath normal skin.

DR MORRISON: There was a strong family history of malignancy in this case.

DR MCCOMBS: Perhaps we should have paid more attention to that.

SUMMARY

DR MCCOMBS: We have presented the clinical history and pathological findings of a case of acute dermatomyositis that was associated with a rapidly growing and diffusely metastasizing "oat-cell" carcinoma of the lung. In retrospect, it is possible to see that many of the clinical features previously described as being commonly present in dermatomyositis were evident in this case, on the other hand, the acuteness of the disease, the lack of significant muscle pain, and the peculiar nature and distribution of the rash prevented this diagnosis from being made before death. We have speculated upon the possible

relationship between the growth of the tumor and the development of the dermatomyositis. The pathological findings seemed to refute this relationship, but the clinical impression remains that the tumor initiated or activated an acute and generalized vascular disorder.

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RECENT ADVANCES IN HEMATOLOGY

HELEN W BELDING, M D * AND JOSEPH F ROSS, M D †

RECENT advances in knowledge of hematologic disorders have led to marked improvements in the practical management and therapy of several serious and puzzling diseases. The etiology of erythroblastosis fetalis has been determined and measures for the control of the disease have been developed. A new hematopoietic factor, "folic acid," has been shown to be effective in controlling the hematologic but not the neurologic manifestations of pernicious anemia. Our understanding of the pathologic physiology of the hemorrhagic diseases has increased, and new agents for the treatment of leukemia have been introduced and give promise of being effective. It is our intention to present the most important aspects of these developments in concise form rather than to present an exhaustive review of the literature, and we shall refer specifically only to the articles which seem most pertinent to each subject.

FOLIC ACID

During the eighteen months which have elapsed since Spies, Vilter, Koch and Caldwell¹ first reported that macrocytic anemia in relapse would respond to synthetic *Lactobacillus casei* factor, it has been demonstrated conclusively that this substance, now known as "folic acid" or "pteroylglutamic acid," will restore to normal the blood of patients with pernicious anemia, sprue or nutritional macrocytic anemia.²⁻¹²

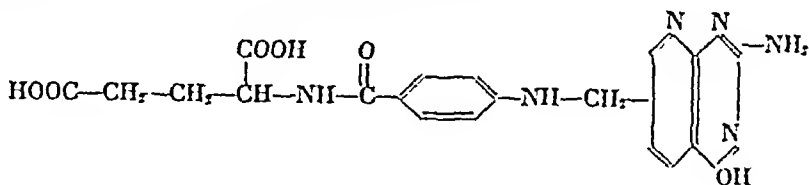
The isolation, chemical characterization and eventual synthesis of folic acid were the culmination of fourteen years of research by independent investigators working with such divergent experimental subjects as bacteria, chicks, monkeys and man. Because of the extreme diversity of these fundamental investigations, many different names have been applied to the substances having "folic acid"-like properties. Thus investigators studying bacterial nutrition called this active principle the "*L. casei* factor", workers investigating the nutritional anemia of chicks called it "Vitamin B₁₂", those studying the nutritional sprue-like syndrome in monkeys named it "Vitamin M", and the

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chemists who derived this active principle from spinach called it "folic acid" (after the Latin *folium* for leaf). Finally the organic chemists, who synthesized this substance, gave it a name descriptive of its chemical structure—"pteroylglutamic acid"¹³



Pteroylglutamic Acid

This substance is present in a variety of foodstuffs rich in the members of the vitamin B complex, e. g., yeast, liver and eggs. The average diet, however, contains very small amounts of folic acid in the simple form illustrated above, since most of the folic acid in these foods is in a combined or "conjugated" form. The fact that folic acid occurs in nature in chemical combination with other radicals suggests why a deficiency in folic acid may arise in certain people who obviously eat folic acid-containing foods. The normal individual, through the action of an enzyme known as "conjugase," is able to "split" the folic acid conjugates and liberate the "free" form of pteroylglutamic acid.¹⁴ This free form is known to be a potent hematopoietic stimulant in contrast to the "inactive" conjugated forms. The individual with pernicious anemia, on the other hand, apparently lacks available "conjugase" and therefore is incapable of breaking down the conjugated forms of folic acid. Such a patient will respond to synthetic preparations of folic acid, however, or if given liver extract will be able to utilize the folic acid conjugates. It is probable that one of the functions of liver extract is to provide some substance necessary for the normal functioning of this particular enzyme system in the body. It appears certain that folic acid is not the active anti-anemic principle contained in liver extract, as the amount of folic acid in liver extract is too minute (0.07-0.3 micrograms per liver extract unit) to produce any hematopoietic effect.

Our present knowledge concerning the role of folic acid in human and animal nutrition is far from complete. However, in view of the fact that the general public has already been told that folic acid offers a "new hope" to patients with pernicious anemia, it seems important that the medical profession become fully acquainted with the very definite therapeutic limitations of this substance.

Folic acid has been found to be an effective hematopoietic agent only in the anemias which are characterized by a macrocytosis and a megaloblastic bone marrow. This group includes pernicious anemia, nutritional macrocytic anemia due to a poor diet, sprue, macrocytic

anemia of pregnancy and the megaloblastic anemia of infancy. Some of the related macrocytic anemias, such as those associated with cirrhosis of the liver or with gastrectomy, have not shown an adequate response to folic acid.¹² Folic acid is of no value in aplastic anemia, myelophthisic anemia, iron deficiency anemia, leukemia or idiopathic leukopenia.

There is no question that folic acid administered to patients with untreated pernicious anemia, in oral doses of 15 to 20 mg daily, will produce rapid subjective improvement, a reticulocytosis and a satisfactory rise in the red blood cell count, hemoglobin, blood platelets and white blood cell count. In other words, it closely simulates the response usually seen in such patients treated with potent liver extract, although the reticulocytosis may be submaximal and the rate of erythrocytic regeneration at times may be slower than with liver extract. Furthermore, it is possible to maintain for at least one year normal blood levels in patients with pernicious anemia, with a daily oral dose of 15 mg of folic acid.^{12, 15}

Undoubtedly the most serious manifestation of pernicious anemia is subacute combined degeneration of the spinal cord ("combined system disease"). That folic acid does not prevent the development nor the progression of this complication has now become evident.^{12, 16} In our own series of twenty-two patients with pernicious anemia treated with folic acid,⁹ three have developed combined system disease and two have shown progression of already existent neurological lesions, even though the hematologic status of all these patients remained essentially normal. Furthermore, the progression of central nervous system damage may at times be far more rapid than is usually observed in untreated patients with pernicious anemia.^{12, 16} An example of the explosive development of combined system disease in a patient treated with folic acid is afforded by the following case.

J S, a 69 year old, white male who had maintained adequate, although not optimal blood levels with liver extract therapy for nine years, was started on monthly intramuscular injections of 30 mg of folic acid. He suffered a severe hematologic relapse in six months' time, but rapidly underwent a remission when the folic acid dosage was changed to 15 mg daily by mouth (Fig 196). For seven months following the institution of folic acid therapy, he exhibited no signs or symptoms of combined system disease, but during the eighth month of therapy, he complained of sudden onset of "heaviness" in the soles of his feet. Vibratory sense was perceptible but moderately diminished in the lower extremities. Three weeks later he was hospitalized with complete vibratory sense loss in the lower extremities and pelvis, loss of position sense, and the inability to stand alone or to hold objects in his hand (Figs 196 and 197). Blood and bone marrow examinations were completely normal at this time and had been so for the preceding two months. After five weeks of intensive intramuscular liver extract therapy (105 units daily),

* Folic acid used in this study was provided by the Lederle Company through the courtesy of Dr S M Hardy.

in addition to folic acid, he was able to walk alone and had regained his position sense and coordination ability. Vibratory sense was not recovered during this time.

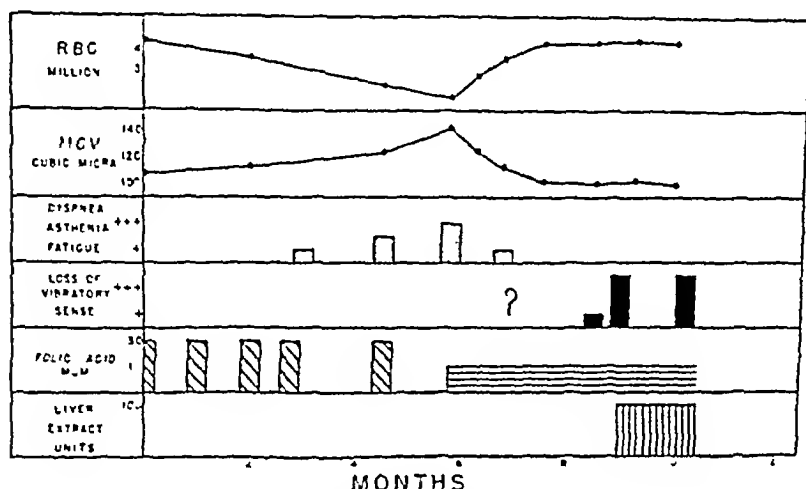
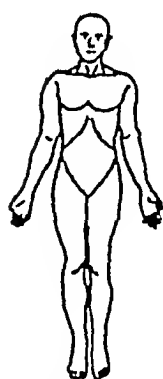
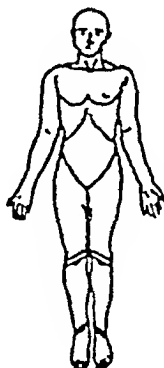


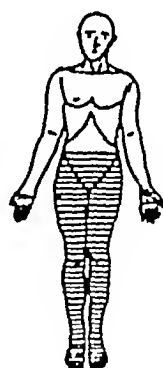
Fig 196 (Case of J S) —Pernicious anemia treated with folic acid



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Fig 197 (Case of J S) —Rapid vibratory sense loss during folic acid therapy

This case illustrates the fact that neurologic damage can rapidly progress despite a normal blood picture, and also that small monthly injections of folic acid are inferior to larger daily oral doses.

At the present time, there are undoubtedly many patients with pernicious anemia who have been maintained in good health with folic acid. However, the very seriousness of combined system disease

and the fact that patients may at any time develop it while under treatment with folic acid, are sufficient reason for stating that no patient with pernicious anemia, other than those under close clinical observation for investigative purposes, should be treated with folic acid as the sole therapeutic agent. There seems to be little rationale for the combined use of folic acid and liver extract in the treatment of these patients, since liver extract alone, in doses of 15 to 30 units every two to four weeks, will effectively control both the hematologic and neurologic aspects of the disease in the vast majority of patients with pernicious anemia. Furthermore, at the present time, liver extract therapy is far more economical than folic acid treatment. The cost of 15 units of liver extract once a month for a period of one year is approximately \$8.00, whereas the present retail price of one year's supply of folic acid, taken in oral doses of 15 mg daily, is nearly \$130.00.

Some of the more dramatic clinical responses to folic acid have been seen in patients with tropical and nontropical sprue^{8, 4, 6, 7}. This chronic disease is characterized by a macrocytic anemia, recurrent episodes of diarrhea and fatty stools, impaired intestinal absorption of fat and carbohydrate, glossitis, weight loss and, at times, peripheral and central nervous system lesions. Liver extract is fairly effective in controlling this disease in some patients, although the response frequently is less complete than in pernicious anemia and requires larger amounts of liver extract. With folic acid treatment, many of these patients have exhibited a striking regression in gastrointestinal symptoms with a disappearance of diarrhea and fat from the stools. Concomitantly, there have been a progressive gain in weight and strength and satisfactory blood regeneration. Many patients who have been totally incapacitated by their disease have been returned to health and are now able to work. The ability of folic acid to maintain permanent remission in sprue has not yet been established. It is probable, however, that in certain patients, in whom the disease is of long standing and in whom certain irreversible changes in the intestine have taken place, complete remission cannot be effected even with folic acid.¹²

The use of preparations containing both folic acid and iron is unnecessary, adds greatly to the expense of medication, and may actually interfere with the evaluation of a patient's response to specific medication. The addition of folic acid to iron does not enhance the therapeutic effect of the iron, since the extent and rate of blood regeneration in patients with iron deficiency anemia treated with a folic acid-iron mixture has not been found to be greater than that expected with iron alone.¹² Furthermore, the majority of patients with macrocytic anemia who will respond to folic acid do not need medicinal iron.

THE RH FACTOR AND ERYTHROBLASTOSIS FETALIS

The clinical importance of the Rh factor is now universally recognized. Early investigations of this factor led to the explanation of certain heretofore unexplained intragroup transfusion reactions¹⁷ but of far greater significance was the correlation between Rh isoimmunization of the mother and the occurrence of erythroblastosis fetalis¹⁸. With our present knowledge it is possible to detect male and female Rh incompatibility, maternal sensitization, and to predict with a fair degree of accuracy the probability that an infant may have erythroblastosis fetalis. Recent studies have led to a more rational and effective method of treatment with the result that there has been a maternal reduction in the death rate of erythroblastotic infants.

Genetics of the Rh and Hr Blood Factors.—The "Rh factor" is an antigenic substance present in the erythrocytes of approximately 85 per cent of the white population. In a broad sense each person inherits two chromosomal Rh factors, one from each parent, with the result that there are three possible genetic classes: the homozygous Rh-positive (RhRh), the heterozygous Rh-positive (Rhrh), and the homozygous Rh-negative (rhrh). Actually the situation is far more complicated than it appears as it is now known that each of these two chromosomal Rh factors represents a gene complex. With the discovery of the several Rh subgroups and the fact that the Rh-negative ("Hr factors") as well as the Rh-positive components are antigenic, the original Rh nomenclature has become confusing and has required constant modification. It would appear only a matter of time until there is universal acceptance of the English concept and terminology, which is simpler and more compatible with the known genetic facts.^{19, 20} This theory postulates three closely linked genes on each of the two inherited Rh chromosomes which may be represented as

D	d	corresponding to the American terminology of	Rh ₀	Hr
C	c		Rh'	Hr'
E	e		Rh''	Hr''

For example, since the Dd location on the chromosomes may be occupied by DD, Dd, or dd (the D gene antigen being detected by anti-D serum and the d gene antigen by anti-d serum), it is possible for an individual to have one of several different combinations (Table 1). In this system any individual with a gene complex which contains D corresponds to one of the four "Rh positive" blood types as designated by the older terminology. The small letters c, d and e are the English counterpart of the so called Hr factors in the Rh nomenclature.

The various Rh blood factors according to both nomenclatures and the possible serologic reactions with respective anti-sera are repre-

TABLE 1
ELEMENTARY ANTIGEN STRUCTURE OF THE RH FACTORS*

Human Rh-Antisera		"Rh-Positive" Factors				"Rh-Negative" Factors			
		Rh ₀	Rh ₁ (Rh' ₀)	Rh ₂ (Rh'' ₀)	Rh ₁ Rh ₂ (Rh' ₀ Rh'' ₀)	rh	rh'	rh''	rh'rh''
Cappell	Weiner	cDe	CD ₀	cDE	CDE	cde	Cde	cdE	CdE
Anti-D	Anti-Rh ^o	+	+	+	+	-	-	-	-
Anti-C	Anti-Rh'	-	+	-	+	-	+	-	+
Anti-E	Anti-Rh''	-	-	+	+	-	-	+	+
Anti-C&D	Anti-Rh ₁	+	+	+	+	-	+	-	+
Anti-D&E	Anti-Rh ₂	+	+	+	+	-	-	+	+
Anti-c	Anti-Ihr'	+	-	+	-	+	-	+	-
Anti-e	Anti-Ihr''	+	+	-	-	+	+	-	-
Anti-d	Anti-Ihr ₀	-	-	-	-	+	+	+	+

* Modification of chart from Cappell (19)
Each genetic combination constitutes one half of the chromosomal make-up of the individual
Factors C and D have also been further subdivided

sented in Table 1. It may be seen that clinically the most important serum is anti-D (anti-Rh₀ or "85 per cent serum"), since most cases of iso-immunization can be resolved by use of this one serum. Although all of the other gene factors are antigenic and may evoke antibody production in a person lacking any one of them, these factors are much less frequently responsible for erythroblastosis fetalis or intragroup transfusion reactions. The detection of the Rh-negative variants (c, d, e) is important in determining whether or not an Rh-positive father is homozygous or heterozygous. Once a mother has been sensitized to the Rh factor and has had an erythroblastotic child, all subsequent children of a homozygous father will be erythroblastotic. On the other hand, approximately one half of the children of heterozygous fathers will be Rh-negative, and knowledge of this fact allows prediction of the possibility of subsequent normal children following an erythroblastotic baby. Knowledge of these factors also has widened the scope of forensic medicine and anthropologic study.²¹

Iso-immunization and Incidence of Erythroblastosis Fetalis.—An Rh-negative individual may become sensitized either by transfusions or injections of Rh-positive blood, or by giving birth to an Rh-positive infant. Evidence as to the precise mechanism whereby the Rh factor in the fetus induces iso-immunization in the Rh-negative mother is as yet inconclusive, although the most widely accepted theory postulates that the fetal erythrocytes gain entrance to the maternal circulation during the latter part of pregnancy through some defect in the placenta.²²

The strongest stimulus to development of anti-Rh anti-bodies is transfusion of Rh-positive blood. Rh-negative females who have been sensitized in this way are far more likely to have erythroblastotic babies than are women who have carried Rh-positive babies.²³

The anti-Rh antibodies of a pregnant woman, developed either in response to blood transfusion or to previous pregnancies, pass across the placenta into the fetal circulation where they destroy the Rh-positive erythrocytes of the fetus and also probably damage tissue cells as well.

It must be stressed that once an Rh-negative individual becomes sensitized to the Rh factor, he or she remains so for life, despite the fact that the Rh antibodies may not be demonstrable in the serum. Transfusion of Rh incompatible blood into an Rh sensitized individual may and all too frequently has resulted in a fatal hemolytic transfusion reaction.

One or both of two types of anti-Rh antibodies may be elaborated by a sensitized individual: simple agglutinins, and "blocking" ("incomplete" or "inhibiting") antibodies. The latter type of antibody has grave prognostic significance when it appears in the serum of a

With the technic that has been described, the numerical values given in Table 1 have served as practical guides in estimating hypoplasia or hyperplasia of the bone marrow and detection of the predominance of one or more types of cells. The figures represent the approximate range and average values of cellular elements which may be expected in the bone marrow samples obtained with normal infants and children. The higher lymphocyte percentages have been noted in infants beyond the neonatal period.

BONE MARROW IN THE ANEMIAS

The Hemolytic Anemias.—The individual cellular constituents in the bone marrow are in such close proximity to each other that it is difficult to affect one element independently of the others. This total stimulation is best observed in the hemolytic anemias and most regularly in acute hemolytic anemia. In the latter, red cell regeneration is associated with an increase in granulocytes and platelets. The reverse occurs in aplastic anemia in which the three cell types are depressed simultaneously. However, other factors must operate in addition to anatomical proximity, since involvement of a single cell type may occur. This is illustrated in hypoplastic anemia in which red cell production is inhibited without equal depression of the other cellular elements. Similarly selective hyperplasia occurs in iron deficiency anemia and in chronic blood loss in which the normoblasts and their immediate precursors alone are primarily increased.

In the group of hemolytic anemias comprising erythroblastosis fetalis, congenital hemolytic jaundice, acute hemolytic anemia, sickle cell anemia and Mediterranean anemia the bone marrow is hyperplastic with an increased proliferation of normoblasts, and to a lesser extent of erythroblasts. Granulopoiesis may be active especially in acute hemolytic anemia. In iron deficiency anemia and in chronic hemorrhagic anemia the bone marrow is similarly hyperplastic, normoblasts are greatly elevated but granulopoiesis is normal. The increase of the nucleated red cells in the hereditary hemolytic syndromes in excess of 50 per cent of all the nucleated elements in the marrow constitutes an important diagnostic feature. In the milder forms of Mediterranean anemia an increase in the erythroblastic elements is similarly observed in the bone marrow but not to the extent observed in the severe forms of this disease requiring periodic transfusions. The resistance to iron salts indicated by the lack of regeneration of hemoglobin in the peripheral blood is reflected in the bone marrow by the persistence of the high normoblastic levels. This serves as a diagnostic criterion since in iron deficiency anemia, with which the less severe forms of Mediterranean anemia are frequently confused, the favorable response to iron therapy results in a drop of the nucleated red cells to normal levels within the bone marrow.

pregnant Rh-negative female, since there is evidence that this type of antibody may be responsible for the more severe forms of erythroblastosis fetalis.¹⁰ Practical methods have been devised for the detection and quantitative estimation of both of these antibodies in the sera of sensitized individuals.^{21, 24, 25}

From the data pertaining to incidence of erythroblastosis fetalis in Table 2, it may be observed that the subject of Rh iso-immunization

TABLE 2

INCIDENCE OF ERYTHROBLASTOSIS FETALIS

	Approximate Frequency	Approximate Percentage
1 Marriage between an Rh-positive male and Rh-negative female ²	1 in 8	12
2 Homozygous Rh-positive persons ²⁷	1 in 2 3	43
3 Marriage between homozygous Rh-positive male and Rh-negative female ²⁷	1 in 18	5 7
4 Pregnancy when fetus Rh-positive and mother Rh-negative ¹⁹	1 in 10	10
5 Sensitization of Rh-negative female married to Rh-positive male ¹⁹	1 in 25	4
6 Erythroblastosis in total births ¹⁹	1 in 250	0 4

is decidedly more complex than the above simplification implies. The lower than expected incidence of erythroblastosis fetalis has been attributed to such factors as the relatively high incidence of heterozygous fathers, the small size of many families, other genetic factors which may influence the production of antibodies, and the variation in the permeability of the placenta to passage of antigen.²² Instances of erythroblastosis fetalis in the firstborn are rare and are usually not without at least presumptive evidence of previous maternal sensitization. In the relatively small percentage of Rh-positive mothers who have borne erythroblastotic infants, sensitization has been due to one of the Rh subtypes other than D²² or more rarely to the blood factor A.²⁰

Management of Erythroblastosis Fetalis.—The three clinical conditions, anemia of the newborn, icterus gravis neonatorum and hydrops fetalis, are all variants of congenital hemolytic disease (erythroblastosis fetalis), and their difference is chiefly one of severity. The presence of the predominant feature of each entity, from which it derives its name, usually makes such a classification possible, although in certain cases there is considerable overlapping. In hemolytic anemia, the mildest form of the disease, recoveries usually occur with treatment or even spontaneously. The majority of infants with icterus gravis survive with treatment,²⁷ although some of these sustain permanent cerebral damage.²³ In the third and most severe form, hydrops fetalis, the result is invariably fatal. The same mother may give birth

to infants with any of the three forms but usually there is a progression in the severity of the disease with each successive pregnancy.

Rh typing of all pregnant women is essential. The husbands and previously delivered children of all Rh-negative women should be Rh typed, and in those women with Rh-positive husbands, tests for detection of Rh antibodies should be started not later than the twenty-fourth week of pregnancy and should be repeated at monthly intervals unless a rising titer of anti-Rh antibody is detected, when studies should be made each two weeks. A high or steadily rising titer of anti-Rh antibodies is strong evidence that the infant will have erythroblastosis fetalis, although this is not invariably true. Also the appearance of blocking antibodies carries a graver prognosis than does the presence of simple agglutinins.¹⁹ The induction of a premature delivery when maternal Rh antibodies are present is not warranted in the majority of cases. Studies of the apparent correlation between duration of fetal exposure to maternal antibodies and prognosis of the newborn have shown that such a procedure is unnecessary when Rh antibodies first appear less than ten weeks antepartum, useless when they have been strongly positive for more than fifteen weeks prior to term, and indicated only in that small group where antibodies first appear ten to sixteen weeks before expected delivery.²⁵ In the latter situation early induction of labor and immediate transfusion of the infant may increase the chances of survival of a moderately affected infant.

Until recently the accepted treatment of the erythroblastotic infant has been to combat the anemia and hemorrhagic tendency by prompt and repeated transfusion of Rh-negative compatible or group O blood. This method has not been wholly successful in many of the severer cases despite the correction of anemia. At the present time it is hoped that the survival of these infants will be increased by means of the so-called replacement transfusion method.²⁶ By repeated alteration of blood removal with administration of equivalent amounts of Rh-negative blood through the umbilical or peripheral vein, it is possible within one hour's time to remove more than 75 per cent of the Rh-positive blood of the infant and to replace it with Rh-negative blood. The rationale of this procedure is to reduce to a minimum the harmful circulating maternal anti-Rh antibody and to remove the Rh-positive erythrocytes of the infant so that they will not be hemolyzed intravascularly. It is as yet too early to determine whether this method is effective in preventing damage to the brain, liver and kidney.

Although there is no specific method of prevention of erythroblastosis fetalis, certain prophylactic measures can and must be observed. Unnecessary sensitization of Rh-negative mothers and the prevention of intragroup transfusion reactions due to Rh incompatibility must

be avoided by transfusing only with Rh compatible blood Preliminary experimental work suggests that in the future antibody neutralization or inhibition of antibody production may be accomplished by chemotherapeutic or immunologic methods^{30, 31}

HEMORRHAGIC DISEASES

With the exception of those bleeding diseases attributable to a deficiency in prothrombin, our present knowledge and the treatment of the hemorrhagic disorders are still in a highly unsatisfactory state. Definite progress has been made in the study of the pathogenesis of some of the more serious of these diseases, however, and there are indications that more effective therapeutic agents shortly may be forthcoming

I Bleeding Diseases Due to Abnormality in the Clotting Mechanism.—Blood coagulation depends upon the conversion of prothrombin to thrombin through the action of thromboplastin and calcium, and subsequently upon the interaction between thrombin and fibrinogen to form the fibrin clot A deficiency in prothrombin, thrombin or fibrinogen obviously will delay or inhibit blood coagulation

A. DEFICIENCY IN PROTHROMBIN—Prothrombin is synthesized in the liver and for this synthesis vitamin K is required³² As prothrombin is normally present in the plasma in excess of the normal physiologic requirement, there is usually no appreciable prolongation of coagulation time nor appearance of hemorrhagic manifestations until the prothrombin level is reduced to below 20 per cent of normal³³ The causes of prothrombin deficiency are fairly well understood and in many instances can be remedied by simple therapeutic measures

1 Prothrombin Deficiency Resulting from Liver Disease—Serious impairment of liver function interferes with the production of prothrombin, and in cirrhosis, hepatitis and yellow atrophy a severe hypoprothrombinemia may develop which frequently results in hemorrhagic manifestations In such conditions the parenteral administration of large amounts of vitamin K (60 mg daily) may be of some value, but the only really effective treatment is to supply preformed prothrombin by transfusions of fresh whole blood or plasma Stored blood is unsatisfactory because of the rapid loss in its prothrombin activity³⁴

2 Prothrombin Deficiency Resulting from Deficiency of Vitamin K—Naturally occurring vitamin K is soluble only in fats, and defective fat absorption will, therefore, result in poor vitamin K absorption and deficient prothrombin production There may be impairment of fat absorption when bile salts do not reach the intestinal tract (e g, in bile duct obstruction), in sprue, and in certain ulcerative or granulomatous intestinal diseases Synthetic vitamin K may be provided in

such cases by parenteral injection or by the oral administration of one of the related water-soluble preparations (synkayvite, lyknone and synkamin). These water-soluble synthetic vitamin K-like substances, given in a dosage of 1 mg daily, are particularly useful in the long-term management of a chronic intestinal disease (e.g., nontropical sprue). Actual dietary deficiency of vitamin K rarely exists except in the newborn infant, since the normal intestinal bacteria are capable of synthesizing vitamin K even when the diet is deficient in this vitamin. The absence of coliform bacteria in the bowel of the newborn infant, together with a low prothrombin level in the maternal circulation, may result in marked hypoprothrombinemia in the newborn. There is now reasonable doubt as to whether this hypoprothrombinemia is directly responsible for the condition known as hemorrhagic disease of the newborn,^{25, 26} but until further evidence is available, the routine administration of 2 mg of vitamin K to the mother several hours prior to delivery, and the routine injection of 2 mg of vitamin K into the newborn infant on the first and second day following delivery, is recommended.

3 Prothrombin Deficiency Resulting from Drugs—(a) Dicumarol—The administration of dicumarol causes a decrease in the prothrombin level of the blood, and for this reason it is used fairly extensively to prevent venous thromboses. Its exact mode of action has not been determined but the best evidence indicates that it depresses prothrombin synthesis by interfering with the liver's utilization of vitamin K.²⁴ The usefulness of dicumarol is limited by the latent period (usually twenty-four to forty-eight hours) between its administration and effect, and the time (several days) required for the return of prothrombin to normal following its withdrawal.²⁵ Dicumarol is usually given in amounts sufficient to reduce the prothrombin level to from 60 to 30 per cent of normal.²⁷ Within this prothrombin range the coagulation time usually is not significantly, if at all, increased. However, hemorrhage has occasionally occurred in patients in whom the prothrombin level has dropped to below 10 per cent of normal.²⁴ Unfortunately it is not possible accurately to control the drop in prothrombin and the danger of hemorrhage may outweigh any beneficial effect. The use of dicumarol is contraindicated in patients with hemorrhagic diathesis, liver disease, subacute bacterial endocarditis, renal insufficiency, or whenever daily prothrombin estimations cannot be performed. Specific treatment for too low a prothrombin level or for an overdose of dicumarol is immediate transfusion of fresh whole blood or fresh plasma and injection of large doses of synthetic vitamin K. An initial dose of 60 mg of vitamin K should be administered by injection whenever the prothrombin level falls below 20 per cent of normal and 30 mg should be given three times a day until the prothrombin time has returned to normal.²⁷ Since there is a delay of

six to twenty-four hours in the action of vitamin K, its effect may not be rapid enough in severe dicumarol poisoning, and transfusion therapy may have to be resorted to. Dicumarol still should be considered a dangerous drug and must be used with extreme caution.

(b) Salicylates—The action of salicylates on the plasma prothrombin concentration is apparently similar to, although less powerful than, that of dicumarol.³⁴ In the past several years conflicting reports have appeared concerning the danger of hemorrhage due to the hypoprothrombinemia induced by intensive salicylate therapy. A recent well-controlled study, however, has pointed out that although hypoprothrombinemia of varying degree (16 to 59 per cent of normal) occurred at some time during the first three weeks in patients with acute rheumatic fever given doses of 10 gm of sodium salicylate daily, the prothrombin spontaneously returned to normal (usually within three days), despite continued salicylate therapy.⁴⁰ It was further pointed out that while a bleeding tendency may become manifest if the hypoprothrombinemia is marked, it promptly ceases with the return of the prothrombin level to normal. Although it has never been definitely established that salicylates are responsible for serious hemorrhage, the prophylactic administration of vitamin K has been recommended whenever surgical operations are contemplated in salicylate treated patients.⁴⁰ It has been stated that approximately 1 mg of synthetic vitamin K is required to prevent the hypoprothrombinemia induced by 1 gm of acetylsalicylic acid.⁴¹

(c) Heparin—Heparin, an effective clot inhibitor by reason of its antithrombic and antiprothrombic activity, is frequently used for the prevention of thrombosis and embolism.³⁴ It produces an immediate increase in clotting time but this effect lasts only about one hour after a single large dose.⁴² For this reason it is frequently used in conjunction with dicumarol. In order to maintain the anticoagulant effect of heparin, it must be given either by repeated intravenous injections or in a slowly absorbable menstruum by subcutaneous injection. Withdrawal of heparin will result in immediate discontinuance of its effect. Should hemorrhage or other complications necessitate abrupt cessation of the anticoagulant effect of heparin, transfusions of fresh whole blood or fresh plasma should be given. An intravenous injection of protamine solution⁴²⁻⁴³ will quickly neutralize the effect of heparin, but protamine itself is a relatively toxic substance and must be given with considerable care.⁴³

4 *Idiopathic Hypoprothrombinemia*—Five cases have been reported in the literature in which episodes of hemorrhage were associated with a severe hypoprothrombinemia not attributable to vitamin K deficiency, liver disease, or poisoning by dicumarol or related substances.⁴⁴ It cannot be assumed, however, that these cases represent a disease entity, as the etiology was never established and there was

considerable individual variation in the age of onset, family history, blood findings and course of the disease

Effect of Digitalis and Penicillin on Blood Coagulation—There is some experimental evidence that digitalis increases the coagulability of the blood.⁴⁵ Reports on this subject, however, have been conflicting and there is insufficient clinical evidence to prove that therapeutic doses of digitalis promote venous thrombosis.³⁹ Furthermore, it should be pointed out that the control of congestive heart failure with digitalis is in itself an important factor in the prevention of thromboembolism.

It has been shown that penicillin produces marked reduction in clotting time.⁴⁶ Whether it is also conducive to thrombus formation has not yet been adequately investigated, but the hope that it might prove an effective blood coagulant in hemophilia has not been realized.⁴⁷

B HEMOPHILIA—The principle feature of this hereditary blood disorder is the marked prolongation of blood coagulation time in the presence of a normal platelet count, normal bleeding time and normal clot retraction. The defect in the clotting mechanism of hemophilic blood is not due to a deficiency in prothrombin, fibrinogen or calcium, nor to increased resistance in the blood platelets.^{48, 49, 50} The plasma of hemophilic patients is deficient in some as yet unidentified substance essential for clot formation. This substance, which is present in normal plasma, has been concentrated in plasma protein fractionation⁵¹ and is presumably associated with the plasma globulin fraction. An intravenous injection of 200 to 600 mg. of this substance temporarily accelerates the coagulation time of hemophilic patients as much as do therapeutic doses of whole blood or plasma.^{49, 50} At the present time, except for its small volume, this substance has no advantage over fresh plasma or blood. Transfusions of fresh whole blood (or plasma) are still the most effective means of controlling hemorrhage in hemophilic patients. The local use of hemostatic globulins or thrombins (which are available commercially) is of considerable value in controlling local bleeding in hemophilic patients and has reduced considerably the hazards of minor surgical procedures and tooth extractions in such patients.

C FIBRINOGENEMIA Fibrinogen deficiency occurs in conjunction with prothrombin deficiency in extensive hepatic disease and can be remedied at least temporarily by blood transfusions. Extremely rare cases of a congenital lack of diminution of fibrinogen have been reported.⁵²

II Bleeding Diseases Due to Deficiency in Blood Platelets—
A Idiopathic Thrombocytopenic Purpura—This disease, usually seen in young adults, is characterized by recurrent episodes of profuse bleeding and purpura, prolonged bleeding time, decreased platelets, normal clotting time, nonretractile blood clot and a positive tourniquet

test The increased bleeding time in these patients is a reflection of two abnormalities a decrease in blood platelets and an abnormality in capillary contractility The importance of the capillary abnormality in this disease is indicated by the fact that serious bleeding may occur even when the platelets are not significantly reduced⁵³ There are two popular concepts as to the cause of the thrombocytopenia in this condition (1) decreased formation of platelets due to the inhibitory effect of a substance elaborated by the spleen,^{54, 55, 56} and (2) increased destruction of platelets by the spleen⁵⁷ At the present time it is not possible to decide whether one or the other or both of these mechanisms is the primary cause of the thrombocytopenia

The bone marrow in this disease is characterized by an increase in megakaryocytes, many of which show changes indicative of diminished platelet formation⁵⁴ An examination of the sternal bone marrow is of importance in demonstrating these changes as well as in ruling out other causes of platelet diminution

Little new in methods of treatment of thrombocytopenic purpura has been offered in recent years Blood transfusions during the acute bleeding stage with splenectomy during remission is the accepted procedure. The deleterious effects of delayed splenectomy in the face of severe and persistent hemorrhage have been stressed,⁵⁸ but because of the obvious danger of such a procedure this opinion is by no means unanimous Splenectomy is not an infallible cure, but it offers symptomatic recovery in about 75 per cent of the cases in which there has been only one episode of bleeding and in approximately 50 per cent of the patients who have experienced several bleeding episodes⁵⁹ The persistence of a thrombocytopenia after splenectomy is common, although this usually is not accompanied by symptoms of purpura

B Thrombocytopenic Purpura Secondary to Other Diseases—Platelets may be depressed by chemical or physical agents, by infections, by uremia, or by bone marrow destruction due to leukemia or cancer Therapy consists of treating the underlying disease and the administration of blood transfusions It is extremely important to differentiate thrombocytopenia due to these causes from idiopathic thrombocytopenic purpura, since splenectomy in the group of secondary thrombocytopenias is extremely hazardous and may even be fatal

III Bleeding Diseases Due to Capillary Abnormalities—Hemorrhagic diseases due to increased capillary permeability may be the result of nutritional defects (vitamin C deficiency), toxic substances (e g meningococcal sepsis) or to unexplained causes The "anaphylactoid" purpuras (e g, Schonlein-Henoch's purpura) are thought to be due to an allergic reaction although this has never been adequately established There are no characteristic blood changes in this type of purpura but in some cases the tourniquet test may be positive

One disease which is being recognized with increasing frequency

is familial thrombasthenia ("pseudohemophilia") This hereditary disease may occur in either sex and is characterized by excessive bleeding from mucous membranes, usually following minor operations⁶⁰ Blood studies vary in different individuals There may be an increased bleeding time or positive tourniquet test, or both It has been shown that the capillaries in this disorder do not contract following trauma⁶¹ Superficial bleeding can frequently be controlled by the local use of thrombin or fibrin foam, but transfusions are usually ineffective in stopping internal hemorrhages

Rutin—This widely publicized vitamin P-like substance has not been effective in controlling the capillary abnormality in patients with idiopathic thrombocytopenic purpura, anaphylactoid purpura or familial thrombasthenia⁶¹ Furthermore, rutin appears to be of little benefit in preventing or controlling the hemorrhages in hypertensive patients⁶²

THE TREATMENT OF LEUKEMIA

Leukemia was first recognized as a clinical entity exactly 100 years ago, but our ability to avert the universally fatal outcome of the disease, or even to prolong the life of its victims, is very little greater now than it was then There is every reason to hope, however, that more effective methods of treatment will soon be available The application of artificially radioactive isotopes and of nitrogen mustards to the treatment of leukemia has furnished promising avenues of research, even though these agents themselves have not produced results very much superior to x-ray therapy or Fowler's solution

Radioactive Isotopes—Radioactive isotopes afford a new method of administering radiation to neoplastic tissue Their effectiveness depends upon two factors—the greater than normal sensitivity of neoplastic cells to the destructive influence of ionizing radiations, and the localization, at least to a partial degree, of the radioactive substance in the neoplastic tissue itself Radioactive phosphorus, the first isotope to be employed for therapeutic purposes, has now been used for the treatment of leukemia for ten years A sufficient number of cases has been treated to allow an adequate evaluation of its advantages and shortcomings⁶³ The initial hope that radioactive phosphorus would be concentrated to a marked degree in leukemic cells and would selectively destroy them has not been realized It is taken up by leukemic cells to a limited extent, however, and eventually is deposited in regions (e.g. bone and lymph nodes) where its radiations do reach and destroy many leukemic cells Radioactive phosphorus has been most effective in chronic myelogenous leukemia and slightly less effective in chronic lymphatic leukemia Monocytic leukemia responds less well, and acute leukemia responds not at all

Patients with chronic myelogenous and chronic lymphatic leukemia

may be maintained in excellent health for periods as long as four or five years with periodic injections of radioactive phosphorus. The response to such treatment is almost identical with the response to well controlled x-ray therapy, but patients receiving radioactive phosphorus never develop radiation sickness. In many instances patients who have become refractory to x-rays may be brought into remission again with radioactive phosphorus. Furthermore, the duration of survival of patients treated with radioactive phosphorus is somewhat longer than the survival of patients treated with x-ray. The preparation of radioactive phosphorus in the uranium piles of the Atomic Energy Commission has greatly reduced the cost of this material, and has made it considerably less expensive than x-ray therapy. It is our belief that eventually radioactive phosphorus will replace x-ray therapy in the treatment of chronic leukemia.

Uncontrolled use of radioactive phosphorus may produce serious complications. Thrombocytopenia, leukopenia and anemia develop in a certain percentage of radioactive phosphorus treated cases and reflect bone marrow depression. Consequently, all cases must be carefully followed with frequent and complete hematologic studies, and the therapy of each patient must be individualized on the basis of the clinical and hematological findings.

Radioactive sodium will also reduce the leukocyte count and induce remission in chronic leukemia in much the same fashion as radioactive phosphorus.⁶⁴ These remissions are produced by general body radiation since radioactive sodium is uniformly and rapidly distributed throughout all of the sodium in the body.

Hahn and Sheppard⁶⁵ have attempted to localize radiation effects in the reticuloendothelial system and in tumors of this system by employing colloidal suspensions of radioactive manganese and radioactive gold. These colloids are more or less selectively deposited in the phagocytic cells of the reticuloendothelial system where they release their radiations. The initial results of this form of therapy have been encouraging, but appear little different from those which would have been obtained with x-ray treatment or radioactive phosphorus.

It is hoped that future developments will lead to the preparation of substances or compounds which will be selectively deposited in and which will selectively destroy leukemic cells. Such a development might well provide for the first time a really satisfactory treatment for leukemia.

Chemotherapeutic Agents—Interest in the chemotherapy of leukemia has been stimulated by the development of a new group of cytotoxic compounds known as "nitrogen mustards."⁶⁶ Only two of these compounds, methyl-bis-(β -chloroethyl)-amine and tris-(β -chloroethyl)-amine have been investigated clinically.^{67, 68, 69} Both compounds were quite effective in the treatment of Hodgkin's disease,

but neither one was of much value in patients with chronic or acute leukemia. However, literally hundreds of related chemical compounds are yet to be synthesized and evaluated clinically, and it seems possible that one or more of these compounds may prove highly effective in leukemia.

Another group of compounds—the urethanes—also holds promise of aiding in the control of leukemia. Paterson, Thomas, Haddow and Watkinson⁷⁰ reported that ethyl urethane in doses of 1 to 3 gm daily for two to four weeks produced remarkable decreases in leukocyte counts, regeneration of red blood cells and clinical remission in patients suffering from chronic lymphatic or chronic myelogenous leukemia. The remissions occasionally were of several months' duration and in several instances a second course of urethane therapy induced another remission. Similar responses have occurred in a small group of cases which we have observed, but we have been impressed by the fact that in several patients the clinical and subjective improvement was not as great as the hematologic response. Ethyl urethane is only one of many urethane compounds. Several of the more complex compounds (e.g., iso-butyl urethane) are known to be far more effective bacteriostatic agents than ethyl urethane and some of these substances well may prove of even greater value in treating leukemia.

SUMMARY

1 Folic acid in adequate dosage administered orally will restore to normal the blood of patients with pernicious anemia, nutritional macrocytic anemia, sprue and the megaloblastic anemia of childhood. Unfortunately folic acid does not prevent the development of subacute combined degeneration of the spinal cord in patients with pernicious anemia, and for this reason folic acid alone should not be used for the maintenance therapy of pernicious anemia.

2 Rh factor incompatibility between mother and fetus is responsible for the great majority of cases of erythroblastosis fetalis, and it is now possible to predict with fair accuracy when the disease will occur in a newborn infant. Replacement of the blood of seriously affected infants with "exchange transfusions" promises to prevent some of the more serious complications of icterus gravis.

3 Most types of hemorrhagic disease can temporarily be controlled with transfusions of fresh whole blood. Vitamin K is of great value in treating certain types of prothrombin deficiency, and splenectomy is still the only treatment offering permanent benefit to patients with idiopathic thrombocytopenia purpura.

4 Radioactive isotopes and new chemotherapeutic agents promise definite improvements in the treatment of leukemia.

Macrocytic or Megaloblastic Anemia of Infancy.—This condition as described by Zuelzer and Ogden¹ is characterized by a normochromic and usually macrocytic anemia, leukopenia, neutropenia and thrombopenia. The bone marrow reveals a megaloblastic type of erythropoiesis and changes in the granulocytes resembling those in pernicious anemia. Cells resembling normal promyelocytes in size showed lobulation and elongation of the nucleus and vacuolation of the cytoplasm. In later stages of development these cells were characterized by persistence of their large size and hypersegmentation of the nuclei. Prompt and complete transformation of the megaloblastic bone marrow into a normal normoblastic pattern occurs with the use of either liver extract or folic acid.

Hypoplastic Anemia (Chronic Congenital Aregenerative Anemia)—During the latter part of the neonatal period a form of anemia which resembles aplastic anemia may be noted. It differs from aplastic anemia in that red cell formation is depressed without equal involvement of the granulocytes or platelets. The clinical course and the blood picture lack the severity and acuteness of aplastic anemia and it has, therefore, been regarded as one of its variants to which the term "hypoplastic anemia" has been applied. It is an aregenerative type of anemia, probably congenital, characterized essentially by a marked reduction in hemoglobin and red cells and is distinguished from aplastic anemia by the fact that except for depression of normoblasts the other cellular elements in the bone marrow may be only moderately affected or unaltered. The platelets and the total number of leukocytes and reticulocytes are only slightly or moderately decreased, and the percentage of each type of white cell is normal. The smear shows an absence of immature white or red cells, and coagulation, bleeding time and clot retraction, and fragility tests are normal. Hypoplastic anemia should be considered when, despite adequate anti-anemia therapy including frequent transfusions, the hemoglobin, red cells and reticulocytes remain at low levels. This diagnosis is confirmed when the poor hematologic response persists for months and years following the neonatal period. Bone marrow aspiration reveals a marked reduction in the number of nucleated red cells as well as an increase in the numbers of primitive cells or hematogones and of eosinophilic leukocytes.

This anemia continues from the neonatal period into late infancy and childhood and is not influenced by any form of anti-anemia therapy except transfusions which must be carried out at frequent intervals to sustain life. In rare instances, splenectomy has been effective in checking the progress of this disease but the indications for this measure have never been well defined. Possibly the analysis of larger groups of cases will reveal that those children will be benefited by splenectomy whose bone marrow on repeated examination

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reveals the constant presence of nucleated red cells notwithstanding their reduced numbers. Although these may be the individuals in whom, with transfusions, the disease ultimately undergoes spontaneous and permanent remission, splenectomy may conceivably expedite its earlier arrest.

Aplastic Anemia.—The peripheral blood in this condition is characterized by a profound anemia, leukopenia, neutropenia and thrombocytopenia. During the course of the disease the bone marrow shows a progressive decrease in the total count so that the megakaryocytes eventually disappear, the myeloid elements and nucleated red cells are greatly reduced and lymphocytes predominate in the smears. Cases with normal or hyperplastic bone marrows have also been observed with the peripheral blood picture of aplastic anemia and this has been interpreted as a maturation arrest or bone marrow block. Quantitative variations in the total nucleated cell count and distribution of the blood elements, may be due to the fact that areas of relatively acellular marrow alternate irregularly with areas of normal or increased cellularity. True aplastic anemia with an acellular bone marrow and the typical blood picture is a rare occurrence in infancy and childhood. Occasionally acute lymphoblastic leukemia in the leukopenic stage may simulate aplastic anemia and diagnosis is difficult without histologic examination of the bone marrow. Sternal aspiration in leukemia will reveal a cellular bone marrow in which the normal nucleated elements are replaced by lymphoblasts and lymphocytes.

BONE MARROW IN DISTURBANCES OF THE WHITE BLOOD CELL SERIES

Leukemia.—Leukemia in childhood may for a considerable period of its course be unassociated with an enlarged spleen, lymph nodes or a leukocytosis so that the true nature of the disease is unsuspected. At a time when the white cells show very few if any changes in the peripheral blood, the bone marrow may be completely replaced by the "blast" cells of leukemia. Frequently a persistent leukopenia which has been interpreted as resulting from the earlier administration of sulfonamides for the treatment of an obscure infection associated with fever may be demonstrated to be leukemia. In this instance, leukemia as diagnosed by sternal aspiration antedated the infection, and examination of the peripheral blood at this earlier period would probably have shown leukopenia, anemia and thrombocytopenia. It is possible, therefore, for chemotherapy to be instituted when the bone marrow is already infiltrated with leukemic cells and when the peripheral blood is free from the disease. The eventual appearance of leukemic cells in the blood is, therefore, coincidental and cannot be ascribed to chemotherapy. The fever is usually associated with super-

imposed infection in the presence of a marked granulocytopenia. The differentiation between agranulocytosis and the leukopenic type of leukemia in these instances depends upon examination of the bone marrow.

Sternal aspiration is also essential for the differentiation of "aleukemic" leukemia from thrombocytopenic purpura and aplastic anemia with which it may be confused in childhood. As a diagnostic feature it should be pointed out that in anemia resulting from direct bone marrow depression or marrow replacement as occurs in leukemia the red cells are both normochromic or normocytic, and anisocytosis, poikilocytosis and achromia are minimal.

Leukemia in childhood is usually of the acute variety and the bone marrow is hyperplastic and reveals infiltration by primitive cells and a marked reduction in the number of nucleated red cells and of megakaryocytes. In spite of leukopenia, diagnosis by bone marrow examination is unequivocal. In the acute type the normal components of the bone marrow are almost completely replaced by lymphoblasts or myeloblasts. Morphological differentiation between these two cell types is difficult since the usual technics such as the reaction with peroxidase stain is of no value. Lymphoblasts may have a more sharply defined nuclear membrane, a coarser chromatin network and a smaller number of nucleoli than myeloblasts but these features are not always detectable. Occasionally the associated presence of substantial numbers of lymphocytes or of promyelocytes suggests a more definitive classification of the predominating immature cells as either lymphoblasts or myeloblasts. Both types of "blast" cells possess certain fundamental diagnostic features which they have in common. They are usually round, large and uniform in size, the narrow zone of the cytoplasm is basophilic, frequently vacuolated and the nuclear pattern is distinctive. Instead of masses of dense basichromatin, such as are found in the mature cells the chromatin stains lightly and is finely granular and stippled or sievelike and shows the presence of nucleoli. Chronic myelocytic leukemia is less frequently observed in childhood and the bone marrow corresponds to the composition of the peripheral blood in the predominance of myelocytes in various stages of maturity and in the small number of myeloblasts. Chronic lymphocytic leukemia is primarily a disease of older individuals and is only rarely encountered in children. Only one of 50 children with leukemia admitted to the children's service of the New York Hospital in the past fourteen years proved to have the chronic lymphocytic type. The bone marrow in this condition is cellular and shows increased percentages of small mature lymphocytes. Its importance in childhood is the close similarity of the peripheral blood picture with a benign hematologic entity known as acute infectious lymphocytosis.

Acute Infectious Lymphocytosis ^{2, 3}—This disease, recently de-

scribed, is characterized by a hyperleukocytosis with a relative and absolute lymphocytosis, and varying degrees of constitutional reaction. This disease is both infectious and contagious and except for infection of the upper respiratory tract there is a paucity of abnormal physical signs such as lymphadenopathy or splenomegaly. The peripheral white count may attain levels above 100,000 per cubic millimeter with normal small lymphocytes exceeding 90 per cent. Elevated blood levels last for approximately two to seven weeks. At the peak of the peripheral leukocytosis, but not always concomitant with it, the bone marrow is highly cellular with an increased number of small mature lymphocytes. These are transient features and are to be differentiated from the constant cellularity and well-marked lymphocytosis of the bone marrow of chronic lymphatic leukemia. In a case of acute infectious lymphocytosis recently observed in a boy of seven years the maximum total nucleated count in the bone marrow reached 282,500 cells per cubic millimeter with 26 per cent small lymphocytes. In this disease, the myeloid elements, nucleated red cells and megakaryocytes are normal in number.

Infectious Mononucleosis—There is no uniformity of opinion as to the appearance of the bone marrow in this disease. Some investigators have reported atypical mononuclear elements, others have found no abnormalities. In four children with infectious mononucleosis examined at the New York Hospital bone marrow puncture in one instance showed the presence of an occasional atypical lymphocyte and in three the percentages of lymphocytes were within the normal range or at the upper limit of normal.

Agranulocytosis.—The widespread use of the sulfonamides and the recent introduction of thiouracil for the treatment of hyperthyroidism have necessitated close observation of the peripheral blood for their toxic effects upon the hematopoietic system. While the incidence of fatal agranulocytosis is greater in adults than in children, toxic reactions occur in lower age groups with sufficient frequency to warrant close watch of the blood.

Examination of the bone marrow permits visualization of the full extent of damage to the myelopoietic cells on the basis of which prognosis and the possible effectiveness of therapy may be considered. The bone marrow usually shows a reduction in the total count of nucleated cells, a depression of the myeloid elements, leaving the red cell precursors and megakaryocytes relatively undisturbed. The pathologic changes in the bone marrow are extremely variable and depend upon the stage of the disease when sternal puncture is performed. Following injury there is a gradual disappearance of the myeloblasts, promyelocytes, myelocytes and metamyelocytes, and eventually of the more mature neutrophilic cells. These elements are replaced in the bone marrow by plasma cells, reticuloendothelial elements and lympho-

cytes Occasionally in this phase a proliferation of myeloblasts occurs During recovery and in the mild form that has not progressed, the less mature myeloid forms reappear and are followed by the segmented neutrophilic cells

Repeated bone marrow studies are required, however, to guard against a sudden shift to an immature level In mild injury both promyelocytes and myelocytes are present and a marked reduction in the more mature elements and an increase in stem cells and in lymphocytes require immediate withdrawal of the drug The prognosis, therefore, is favorable if moderately normal numbers of granulocytes are observed in the marrow, and unsatisfactory if only lymphocytes and plasma cells are present⁴

Since the return to a normal marrow precedes liberation of mature granulocytes in the peripheral blood, prognosis⁵ depends on the cellular composition of the marrow Except for antibacterial agents such as the sulfonamides⁶ and of penicillin⁷ the effectiveness of the drugs usually prescribed for treatment of agranulocytosis must be correlated with the myelopoietic content of the marrow

With the administration of penicillin to combat infection and withdrawal of the offending drug, recovery from agranulocytosis is probably spontaneous and depends upon the ability of intrinsic factors supplied by the individual to stimulate granulopoiesis

BONE MARROW IN DISTURBANCES OF THE PLATELETS

Thrombocytopenic Purpura.—Bone marrow examination serves to differentiate thrombocytopenic purpura from leukemia and aplastic anemia in which a tendency to bleed occurs It reveals in addition the cellular response to the loss of blood, the megakaryocytic content and the extent of platelet formation Quantitative estimations of the megakaryocytes are carried out in the counting chamber in the course of the total bone marrow count and cytologic study in the fixed smear permits the differentiation of their precursors In a limited experience megakaryocytes in normal children number under 100 per cubic millimeter and usually range from 10 to 35 This estimate should, however, be checked by inspection of the fixed smear to avoid a false impression of megakaryocytic hypoplasia or aplasia Megakaryocytes are readily identified as the largest cells in the bone marrow and mature forms possess a large violet staining multilobulated nucleus and lightly staining basophilic cytoplasm containing fine azurophilic granules Platelets may be observed in the process of separation from the cytoplasm and detached groups are often noted in the immediate vicinity of the mature cells

In essential thrombocytopenic purpura the megakaryocytes are conspicuously increased, with values ranging from approximately 200 to 300 per cubic millimeter. In fixed smears immature forms of mega-

karyocytes are also present which possess a dense nonlobulated nucleus with scant deeply basophilic cytoplasm possessing few granules and occasionally vacuoles. The striking feature of the smear is the hyperplasia of the megakaryocytes and the decreased development of platelets from the adult or young forms. During the period of active purpura the total bone marrow count and the number of nucleated red cells are also frequently elevated. Acute thrombocytopenic purpura occurs more commonly in infants and children while the chronic form occurs generally in adults.

The spontaneous recovery in children is reflected dramatically in the bone marrow by the drop in the number of megakaryocytes to normal levels and restoration of platelet formation. Although the disease is usually self-limited and recovery in children is customary, chronic purpura may find its inception at this age period. Limarzi⁹ recently pointed out that in the acute phase of thrombocytopenic purpura younger forms of megakaryocytes are numerous and that in the less acute and chronic phases the majority are of the adult type with abundant azurophilic granules in the cytoplasm. Following splenectomy, the megakaryocytes revert qualitatively to normal but a moderate hyperplasia of these cells persisted. Dameshick and Miller⁹ recently confirmed by quantitative studies the remarkable restoration of platelet development by the megakaryocytes following splenectomy.

It has been repeatedly demonstrated⁸ that splenectomy is contraindicated in cases of idiopathic thrombocytopenic purpura in which the bone marrow shows a megakaryocytic aplasia. Whereas favorable results have followed splenectomy with megakaryocytic hyperplasia in the bone marrow, failure of improvement following this operation has been correlated with depletion of megakaryocytes in the bone marrow.

Certain instances of chronic thrombocytopenic purpura in children with a diminished number of megakaryocytes in the bone marrow are undoubtedly stages of hypoplastic or aplastic anemia in the course of development. One of these conditions, rather than idiopathic purpura, is to be suspected when the total bone marrow count is consistently reduced despite the normal or increased percentage of normoblasts. A drop in hemoglobin and in red cell values that is not commensurate with the extent of bleeding necessitating frequent transfusions serves as an additional clue to the true nature of the disease.

BONE MARROW IN MISCELLANEOUS DISORDERS ASSOCIATED WITH SPLENOEGALY

Banti's Syndrome (Congestive Splenomegaly).—Limarzi and his associates¹⁰ have differentiated the stages in the cellular reaction of

the bone marrow in Banti's syndrome and closely allied conditions which serve as a guide in the selection of patients for splenectomy. They noted myeloid hyperplasia in the marrow in the earliest stages when the peripheral blood showed a moderate anemia and leukopenia. Later the marrow findings consist of a "maturation arrest" of the myeloid and megakaryocytic tissue with leukopenia, neutropenia, thrombopenia and myeloid immaturity in the circulating blood. In the last stages in which liver cirrhosis has developed, the bone marrow reveals the added feature of an early normoblastic hyperplasia. According to these authors splenectomy offers the best prognosis for restoration of the blood to normal in the first two stages of bone marrow alteration and the least promising in stage of erythroid immaturity.

Primary Splenic Neutropenia.—Wiseman and Doan¹¹ have described a newly recognized syndrome characterized by marked peripheral neutropenia and splenomegaly. Varying degrees of hemolytic anemia and thrombocytopenic purpura may also be encountered. The bone marrow shows a hyperplasia for the myeloid series and, if hemolytic anemia is pronounced, for the erythroid series as well. The spleen in this condition is regarded as the site of abnormal phagocytosis of granulocytes and perhaps as exerting an inhibitory function on the marrow, thus preventing the delivery of these cells to the peripheral blood.⁴ Splenectomy corrects the neutropenia and coincidentally restores other affected blood elements to normal.

Diseases of Lipoid Metabolism.—*Gaucher's Disease*—The sternal marrow reveals large distinctive cells which are oval or elongated and contain one or more small dense nuclei eccentric in position. The cytoplasm is grayish white, presents a wrinkled appearance and is characterized by a finely striated or fibrillar structure.

Niemann-Pick's Disease—Microscopic examination shows infiltration of the bone marrow with foam cells.¹² These are large, more or less rounded, occasionally oval or polyhedral cells containing one or two nuclei often eccentric with loosely arranged chromatin material. The abundant cytoplasm is filled with refractile lipid droplets giving a web-like or honeycombed appearance. Unlike the Gaucher's cells, the foam cells of the disease are readily detected in the counting chamber and can be separated from the megakaryocytes.

BONE MARROW NEOPLASMS

Metastatic neoplastic cells are occasionally observed in the smears obtained by sternal puncture. In *neuroblastoma*, clusters of primitive cells are observed in the counting chamber which are identified in the films as relatively large immature cells forming syncytial masses simulating a mosaic pattern as described by Kato and Wachter.¹³

Multiple myeloma occurs infrequently in childhood¹⁴ and sternal marrow aspiration reveals characteristic large plasma-like cells.¹⁵ The

bone marrow should be carefully scrutinized for metastatic tumor cells when the peripheral blood presents the leuko-erythroblastic reaction which characterizes space-occupying lesions of bone marrow¹⁶

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MANAGEMENT OF THE ASTHMATIC ATTACK IN CHILDHOOD

BRET RATNER, M D *

CAN a child die during an attack of asthma? May such a death result from faulty treatment? These are questions always posed when asthma is the subject of discussion. Because of the anxiety and fear engendered in the parent and child by an attack of asthma, this syndrome appears in the forefront of emergency practice, and the symptomatic therapy of the asthmatic attack is therefore of great interest to the physician.

First, I should like to emphasize the fact that amongst the most serious errors I encounter are overmedication and a bad choice of drugs.

CHOICE OF DRUGS¹

Adrenalin (Epinephrine).—A child should never be given an injection of adrenalin of more than 2 or 3 minims. It should be given subcutaneously or intradermally and never intravenously or intramuscularly. There is no objection to the repetition of the same small dose at intervals of twenty to thirty minutes.

Effect of Large Doses.—If the aim is to produce relief of bronchiolar spasm, small amounts produce the desired effect. Large amounts only tend to cause a further bronchiolar constriction.

The other deleterious effects of large doses (0.5 to 1.0 cc) are (a) the enhancement of apprehension, (b) acceleration of pulse, (c) rise in blood pressure, (d) pounding headache, (e) cardiac syncope, (f) pallor. The result to the patient is the superimposition of a greater feeling of disaster than he is already experiencing from the asthma, and an increase in pulmonary vascular congestion.

Adrenalin in Oil.—The use of adrenalin in oil has been advocated to allay the bad effects of large doses and for prolonged action. I see no need for such a therapeutic agent in children.

Adrenalin is not a drug that can be used for a long-range effect. It either works promptly or not at all. It is only effective in the alkaline pH of the blood but a short time, for it retains its potency only in an acid pH.

An additional fact to be borne in mind is that an oleoma may result from the injection of this combination, which oil tumor may have to

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be excised because it has a tendency to continue to destroy tissue and grow larger

Adrenalin (1 I 00) Inhalation—If the premise, that the action of adrenalin is immediate, is correct, then one or two series of inhalations should be sufficient for relief of an attack of asthma. In my experience, when a patient is given an inhalation outfit he tends to use it excessively. I have therefore come to regard this procedure as a dangerous one and forbid its use for the following reasons:

1 Epinephrine is a habit-forming drug and inhalation is probably the most habit-forming type of therapy because the simplicity of administration tempts the patient to reach for it at the slightest provocation. I do not use the term "habit-forming" in the same sense that we speak of addiction to morphine, but rather to imply that, since a patient does get relief in certain acute seizures, he is tempted to administer it to himself for its stimulating effect when it may not be altogether necessary. It gives the patient a "lift." I recently had a child of twelve who was so dependent upon it that she inhaled adrenalin every night before retiring for fear that she might otherwise suffocate. It took four months to rid her of the habit. She now states that at times she really misses the exciting stimulus it gave her.

2 Since there is no control of dosage an unusually large amount may be absorbed, and the consequences may be serious. Benson and Perlman² of Portland, Oregon, recently reviewed a series of more than a thousand chronic asthmatic cases and reported that death occurred seven to eight times more frequently amongst those who used adrenalin inhalation.

Ephedrine.—What has been said relative to the action and over-dosage of epinephrine holds for ephedrine as well, though to a lesser degree. It must be remembered, however, that thoughtless and excessive use of ephedrine in nose drops may result in the absorption of large amounts. Ephedrine sulfate should be prescribed for a given attack and only several doses be advised. Nose drops should also be prescribed in small amounts and limitation put upon their use.

Syrup of Ipecac—Its Use in Refractory Asthma—In 1939, I published a study on experimental asthma in the guinea pig.³ As a result of these studies, I have come to the conclusion that asthmatics may be divided, broadly speaking, into two groups: (1) those suffering from asthma due to a bronchiolar spasm, and (2) those suffering from asthma due to a bronchial obstruction. The classification is not rigid and one individual may present both types. The bearing that this classification has on the drug therapy of severe asthmatic attacks, and particularly status asthmaticus, is the point of emphasis.

In the bronchiolar spasm type, the antigen reaches the bronchioles via the blood stream and adrenalin will work like a charm. We find this type in food-sensitive cases, and it is the one often encountered in

early childhood The same form occurs in serum-sensitive patients following an injection of specific serum, and it is relieved by adrenalin if the shock is not too profound

Let us now turn to the child who is given injection after injection of adrenalin without the slightest relief Why doesn't adrenalin help? What about the child who has been in a state of status asthmaticus for several days? The answer as I see it is that in such cases it is not the bronchiolar spasm that is predominantly at play, but an edematous state of the lumina of the bronchi with marked bronchial plugging This we learned from our guinea pig experiments When the animals inhaled antigenic dusts, the allergen, coming into direct contact with the lining and vessels of the larger air passages, produced edema and increased secretion, which resulted in obstructive symptoms On the other hand, in anaphylaxis after intravenous injection the allergen, coming in contact with the smooth muscle of the terminal bronchioles, produces a bronchiolar spasm The object lesson is evident. If a bronchiolar spasm is the cause of the symptoms, the administration of adrenalin will bring about relief If no relief ensues from repeated injections of adrenalin, then we must be dealing with an obstructive bronchial asthma due in all probability to some inhalant allergen which has entered the air passages directly Cease adrenalin administration and order some syrup of ipecac

For infants and young children give $\frac{1}{2}$ to 1 teaspoonful, if this does not induce emesis, give 2 teaspoonfuls For older children and young adults, repeated doses may be given until the desired result is produced Follow the ipecac with lukewarm water to further its effectiveness If this therapy is effective, the result is brilliant because relief from distress follows quickly upon the release of the plugs

The explanation for such therapy is simple Because of the ease with which very small particles, or even quite large objects gain access to the respiratory tract, and because exudates can accumulate within it, there arises the necessity for freeing the tract from such obstructions and irritants To this end, Macklin⁴ points out, three mechanisms have developed (1) the cough reflex, (2) the action of cilia, and (3) a wave motion said to resemble peristalsis These three often work together According to Gunn,⁵ the cough reflex functions in the upper airway, the cilia act as far down as the finer bronchioles, while "peristaltic" movements evacuate the entire tract, even including the airway terminals Thus, these activities overlap, the upper part of the airway having all three, the intermediate part two, while the terminals would have only one mechanism for evacuation—namely, that of "peristaltoid" motion The peristaltic movements are brought into play only under abnormal conditions, such as the ejection of masses of thick exudate from the respiratory lumina The "peristaltic" wave in the bronchial tree is said to resemble the reverse peristaltic wave in

the digestive tract, and the speed is too rapid to be accounted for by ciliary action Reinberg⁶ describes it as "tracheal vomiting," and Bullowa and Gotthieb,⁷ as "bellows-like" I prefer the former

It is obvious that the ipecac which causes the nausea, retching, and vomiting, and the irritation caused by the presence of the foreign material in the air passages, hasten and increase peristaltoid action This "tracheal vomiting" releases the obstruction, which under ordinary circumstances might not be released for days

Opiates.—I shall not dwell on the use of opiates, but I should again like to go on record as stating that the use of morphine in asthma is little short of criminal Besides its inhibitory effect on the respiratory center, it also causes a bronchoconstriction I can see no reason for its use and believe that most deaths from asthma have been directly or indirectly due to its use This is supported by the study of Huber and Koessler⁸

Histamine and Histaminase.—As to histamine and histaminase, I should also like to go on record as stating that not until it is more adequately proved that histamine plays a dominant role in asthma shall I regard its use or the use of its antienzyme, histaminase (Torantil), as of truly significant value There is still too much mysticism surrounding the histamine concept of allergy, and its soundness is seriously questioned by many That histamine may be increased in allergy is true, but whether such an increase is in any way related to its causation is questionable It may merely be an end product of disturbed physiology

Aminophylline—This drug has undoubted value in the treatment of asthma in childhood It is more useful in the chronic type of adult asthma and should be given intravenously, or given intramuscularly with 1 or 2 per cent procaine Its value lies in relieving arteriolar spasm and vascular congestion of the bronchi

So-called Antihistaminic Drugs, Benadryl and Pyribenzamine—These newer anti-allergic drugs are of great value in relieving nasal symptoms and urticaria, but have been found wanting in the treatment of asthma They are contraindicated in severe asthma or status asthmaticus because of their marked soporific effect, for which reason they may at times be as deleterious as opiates Furthermore, the drying effects of these drugs on the already dehydrated mucous membranes of the bronchi would tend to aggravate the obstruction by the thickened secretions which are found in all cases of status asthmaticus

MANAGEMENT OF THE ASTHMATIC ATTACK

1 Give small doses of adrenalin (1:1000), 2 to 3 minims, subcutaneously Repeat, intracutaneously, if necessary, two or three times at intervals of twenty to thirty minutes

2 If adrenalin is not effective, give syrup of ipecac by mouth, 1

teaspoonful to 1 tablespoonful, depending on the age of the patient and his response. Follow with lukewarm water to produce emesis.

3 As adjuvants (a) give the patient an enema, (b) remove patient from the bedroom into another room and prop him up in a chair, (c) be sure patient is well protected, then open windows and if not enough air is circulating in the room turn on an electric fan, directing the current of air on the child, (d) burn asthma powders. Be sure that all persons attending the child assume a cheerful attitude to give the child encouragement.

4 Unmedicated steam inhalation is an important adjuvant.

5 If the attack is severe and prolonged, the ipecac emesis should be followed by

(a) Ten to 15 per cent intravenous glucose by slow drip infusion (300 cc for young children, and 500 to 1000 cc for older ones). This is an important procedure, because it allays dehydration, which is usually pronounced, and also reduces edema.

(b) A rectal retention dose of some sedative, such as bromides (10 to 15 grains), phenobarbital ($\frac{1}{2}$ grain), chloral (2 to 7 grains), of ether in oil (1 to 2 teaspoonsfuls in 1 to 2 ounces of olive or Mazola oil). The sedative may also be given by mouth in the form of triple bromides (5 to 15 grains), phenobarbital ($\frac{1}{4}$ to $\frac{1}{2}$ grain), amytal ($\frac{1}{2}$ grain), and/or acetyl salicylic acid (5 to 10 grains). This sedation may be repeated in two or more hours.

(c) Oxygen therapy is soothing and reassuring, but under no circumstances should the patient be put under an oxygen tent, for claustrophobia is very pronounced during severe asthmatic seizures. It is for this reason that a gentle breeze from a fan is also reassuring.

6 The status asthmaticus patient, having relieved himself of the obstructive plug and been soothed by the intravenous infusion of glucose and sedative, usually falls into tranquil sleep. The nurse or parent may be left to watch over the patient (he should not be left unattended), with an order for a repetition of the ipecac and additional sedation if necessary.

After the attack, a salt-free diet should be given, high in carbohydrates. Plenty of liquids, particularly the cola drinks and other sweet beverages, should be prescribed. The salt-free, high carbohydrate, and liquid diet is supportive and increases diuresis, tending to rid the body of the offending allergens.

All of these measures can readily be carried out in the home. However, if it is deemed wise under certain circumstances to remove the child to the hospital, there is no danger in doing it if the child is well protected. Indeed, sometimes when children are moved to another room, or while they are being transported to the hospital, the asthma clears up. This would indicate that an environmental factor is involved.

Once the attack is relieved, I am sure we will all agree that the offending substances underlying the disease should be ferreted out

In conclusion, I should like to comment that if the child is breathing forcefully during the attack and is not cyanosed, the doctor has little to fear. The harder the patient breathes the better. If a child is cyanosed and his breathing is shallow or is apneic, the situation is dangerous. If the sounds on auscultation are clear, loud and resonant, with sibilant and sonorous rales, the asthma is of no serious consequence. If auscultation, on the other hand, discloses feeble sounds and there are moist rales, the seriousness is real. If the rales break through after coughing, it is indicative of moderate bronchial plugging. A rise in body temperature may occur in the asthma of childhood, do not be misled and change the diagnosis to pneumonia. However, it is equally important to diagnose pneumonia if it is present, even in the presence of asthma, for only in this situation should sulfonamides or antibiotics or aerosol penicillin be used. Fluoroscopy or x-ray is an important aid in the differential diagnosis of superimposed pneumonia.

The keynote, therefore, of the treatment of the asthmatic attack (probably with the exception of the emesis produced by ipecac) is gentleness of therapy, with the aim to correct the physiologic disturbance encountered.

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CONGENITAL AORTIC AND SUBAORTIC STENOSIS WITH ASSOCIATED ANOMALIES OF THE AORTA

A GRISHMAN, M D,* M F STEINBERG, M D, F A C P,† AND
M L SUSSMAN, M D, F A C R‡

INTRODUCTION

RECENT advances in the surgical therapy of certain congenital heart defects—ligation or division of patent ductus arteriosus, resection of coarctation of the aorta and the anastomosis of the systemic and pulmonary arterial circulations in tetralogy of Fallot^{1 2 3 4 5 6}—have greatly enhanced the need for precise diagnosis in this field. It has also been found that the frequency distribution of congenital cardiac lesions in clinical material differs from that derived from postmortem data, probably because the latter includes large numbers of conditions incompatible with life beyond infancy or at most early childhood.^{7 8} It has become desirable, therefore, to re-evaluate diagnostic criteria as sufficient clinical material is accumulated in any group of congenital cardiac defects. The following report is based upon twenty-three cases of aortic and subaortic stenosis which we have been privileged to study.

A review of the literature leads to the assumption that aortic and subaortic stenosis are among the uncommon varieties of congenital heart disease. This is not in keeping with clinical experience and can be ascribed partly to the teaching that aortic stenosis in youth is regularly to be considered rheumatic in origin in spite of the lack of a clear history of rheumatic fever or due to degenerative calcific disease in older patients and partly to confusion of these lesions with isolated interventricular septal defect or with patent ductus arteriosus.^{7 8} Indeed, one of our patients had been subjected to surgical exploration elsewhere with the preoperative diagnosis of patent ductus arteriosus.

DIAGNOSIS

Previous Experience.—According to Brown¹⁰ the diagnosis of congenital aortic stenosis is based on the following points

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A review of the literature leads to the assumption that aortic and subaortic stenosis are among the uncommon varieties of congenital heart disease. This is not in keeping with clinical experience and can be ascribed partly to the teaching that aortic stenosis in youth is regularly to be considered rheumatic in origin in spite of the lack of a clear history of rheumatic fever or due to degenerative calcific disease in older patients and partly to confusion of these lesions with isolated interventricular septal defect or with patent ductus arteriosus.^{7, 8} Indeed, one of our patients had been subjected to surgical exploration elsewhere with the preoperative diagnosis of patent ductus arteriosus.

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1 The patients are often of small stature to the extent even of dwarfism. There may be often visceral abnormalities. Pallor is common. However, where the degree of aortic stenosis is slight, these changes may be minimal.

2 The heart is slightly enlarged and the apex beat forcible. There is a systolic thrill at the base which may be felt in the neck. A harsh systolic murmur is heard over the precordium. Both thrill and murmur are of maximum intensity in the second right space. The murmur is transmitted along the great vessels. In 28 per cent of Gallavardin's cases of so-called "pure" aortic stenosis a diastolic murmur was present but no peripheral signs of insufficiency. The aortic second sound is diminished or absent.

3 Pulsus tardus is present and the blood pressure is low. The pulse may therefore be small as contrasted with the forcible apical beat.

4 Roentgen examination may show some hypertrophy of the left ventricle. The ascending aorta is often dilated, the aortic knob small.

5 The electrocardiogram shows normal or left axis deviation.

6 The lesion is frequently completely asymptomatic or well tolerated but syncopal attacks may occur on exertion or anginal pain may be provoked by effort. Infective endocarditis may occur and there is a distinct liability to sudden death.

In connection with subaortic stenosis, Brown points out the association with aortic valvular stenosis (double aortic stenosis), anomalies of the valve cusps, defects of the interventricular septum and hypoplasia of the aorta. Coarctation of the aorta also has been noted.^{11 12 13} He points out that dilatation of the aorta distal to the lesion may occur.

In contrast to aortic stenosis¹⁰ even in the severe subaortic lesions, peripheral signs of aortic stenosis may be lacking. The cases do not show the same tendency to underdevelopment. Although commonly asymptomatic there may be shortness of breath on exertion, precordial pain and sometimes convulsions, presumably due to cerebral anemia. While the physical signs are considered essentially the same as those of the valvular stenosis except that the aortic second sound is not diminished, the pulse is said to be of normal volume. The blood pressure may be normal or low. Brown considered this lesion therefore as essentially benign except for the accident of infective endocarditis and the rare risk of syncopal attacks and sudden death.

Present Experience.—Our present series of twenty-three cases of aortic and subaortic stenosis give the following findings:

1 **Murmur.**—A loud, harsh systolic murmur and thrill radiating along the large arteries but maximal in the right second space was characteristic. However, the murmur might be maximal almost anywhere along the line between this point and the apex. In several of our cases, the maximal intensity was over the mid sternum and occa-

sionally it was lower and to the left, at Erb's point. Confusion with the murmur of interventricular septal defect is understandable. In all cases, therefore, which present a loud systolic murmur over the base or the mid or lower sternum the possibility of aortic or subaortic stenosis must be investigated.

2 *Aortic Second Sound*—Although commonly thought to be diminished or absent, in our experience this was the exception rather than the rule. Both auscultatory and phonocardiographic evidence indicate the second aortic sound to be normal or accentuated (increased amplitude) in most of our cases. When the murmur extends throughout systole, the second sound may fuse with it and may therefore be indistinguishable to the ear. Variations in the intensity of this sound, in our opinion, cannot be used in the differential diagnosis of aortic valvular from subaortic stenosis. On the other hand, a valid criticism of our data may be offered on the basis that only three of our twenty-three patients were subjected to postmortem examination.

Soft, short diastolic murmurs were heard and recorded in about one third of our cases, which conforms to the observations of Gallavardin. There were no peripheral signs of aortic insufficiency.

3 *Blood Pressure*—These readings were most frequently similar to those found in cases of acquired aortic valvular stenosis. The systolic pressure was low and the pulse pressure small.

4 *Arterial Pulses*—The need for careful palpation of the arterial pulses is particularly brought out in these conditions. The systolic thrill and murmur were often palpable in the innominate and carotid arteries. However, the configuration of the pulse tracings recorded over these vessels was the most important single diagnostic sign. The characteristic finding of obstruction to the outflow tract of the left ventricle is revealed in these tracings, viz., a slow initial rise, an anacrotic notch, systolic vibrations and a systolic plateau.

5 *Electrocardiograms* showed either normal or left axis deviation.

6 *Roentgen examination* revealed varying degrees of left ventricular enlargement. The ascending aorta often was prominent, its convexity to the right was increased. Marked dynamic pulsations were frequently noted.

7 *Angiocardiography* did not demonstrate the stenotic zone clearly except possibly in one case (IV) in which a definite infravalvular irregularity was seen. We hope that roentgen exposures made in predetermined phases of the cardiac cycle will assist in this demonstration.¹⁴ Of great interest, however, was the frequent finding of associated abnormalities of the aorta. The prominence of the ascending aorta seen by conventional roentgenography proved to be due to poststenotic dilation (Cases II, V, VI) and is comparable to poststenotic pulmonary artery dilatation which occurs in about one half of the cases of pulmonic stenosis.⁷ However, narrowing and angular de-

formity of the aortic isthmus also was encountered. In Case VI, the narrowing was marked enough to produce the hemodynamics of coarctation. In this case, the unusually low blood pressure in the patient's arms (for a case of coarctation) could be accounted for on the basis of aortic or subaortic stenosis.

8. While there is no doubt that many cases of aortic and subaortic stenosis are asymptomatic or the patients live a reasonably unrestricted and full life, our experience would lead us to emphasize the morbidity to a greater degree than have previous authors. Of our twenty-three patients, three are dead. The ages at death were 4, 9 and 48 years. Furthermore, a careful history often called attention to precordial or epigastric pain on exertion, syncopal attacks and dyspnea on exertion. Electroencephalographic evidence of cerebral anoxemia was recorded in one case. Subacute bacterial endocarditis, however, was uncommon, occurring in only two cases. Clubbed fingers were present only in these.¹⁶

ILLUSTRATIVE CASES

The following cases were chosen for illustrations of the conclusions in the previous sections.

Case I. Typical Aortic Stenosis. No Associated Anomalies

H. B. is a boy of 8. His delivery was normal. His cardiac murmur was discovered in early infancy during a routine examination. At no time has he been physically disabled, short of breath or cyanotic. However, because of his murmur

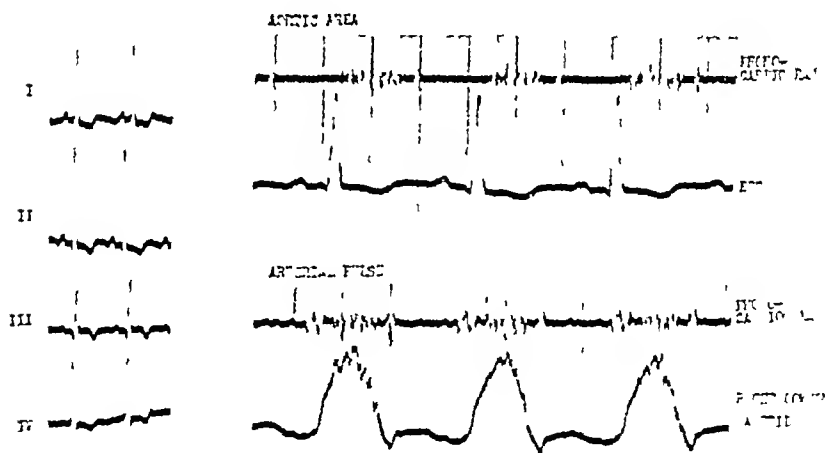


Fig. 69 (Case I) —Typical aortic stenosis, no associated anomalies. The electrocardiogram suggests left ventricular enlargement. Phonocardiogram recorded over the aortic area reveals a systolic murmur of high amplitude and a normal second aortic sound. The carotid arterial pulse tracing shows a slow rise, anacrotic notch, plateau and systolic vibrations.

his physical activities have been restricted. He always is very pale. His mental and physical development is normal.

On physical examination the patient showed marked facial pallor. The heart is enlarged to the left, the apical impulse broadened and heaving. A coarse systolic thrill is felt over the aortic area and of lesser intensity over the carotid arteries. A loud, coarse and high-pitched systolic murmur is best heard over the aortic area. The second aortic sound is well defined and of normal intensity. The blood pressure is 94/70.

The electrocardiogram shows regular sinus rhythm, no axis deviation. The QRS complexes are of high voltage. RT 1, 2 and 4, are depressed and the T waves are inverted in all leads. These changes indicate left ventricular enlargement. The auscultatory findings are confirmed by phonocardiographic examina-



Fig 70 (Case I) —The heart is enlarged to the left and the apex is displaced downward. The angiogram reveals no abnormality of the aorta. (The arrow indicates the level of the aortic valve.)

tion. An arterial pulse tracing recorded over the right common carotid artery shows a slow rise, an anacrotic notch, systolic vibrations and a plateau (Fig 69).

By fluoroscopy the heart is seen to be considerably enlarged to the left, the apex being displaced downward. No abnormal pulsatory phenomena are observed. Angiocardiography reveals a moderate left ventricular hypertrophy and dilatation as the single positive finding (Fig 70).

Case II Aortic Stenosis Dilated Ascending Aorta. Anomalies of the Aortic Arch

C. R. is a 33 year old man. His father is a physician who discovered that the patient had a cardiac murmur at 10 months of age. At that time until referred for examination the diagnosis of patent ductus arteriosus was entertained. The patient, himself a physician, was very active professionally and in sports, including handball, swimming and skiing. In January, 1941, he experienced a severe attack of precordial pain and pressure lasting more than fifteen minutes. Since then he has had frequent anginal attacks and precordial pressure, necessitating a marked reduction of his professional activities. Occasionally, the patient's anginal attacks are relieved by walking.

On physical examination he appears to be well developed. The cardiac dullness is enlarged to the left, the apical impulse broadened and heaving. An intense, coarse thrill is felt over the aortic area and arteries of the neck. Auscultation revealed a very loud systolic murmur best heard over the aortic area and transmitted to the carotid arteries. The second aortic sound appears to be of low intensity, being closely followed by a prolonged decrescendo, almost musical diastolic murmur. Phonocardiographic examinations confirmed the auscultatory findings (Fig 71). Blood pressure was 142/92 mm. The electrocardiogram reveals regular sinus rhythm, left axis deviation and shows inverted T waves in the standard leads (Fig 71). These changes suggest left ventricular enlargement. A pulse

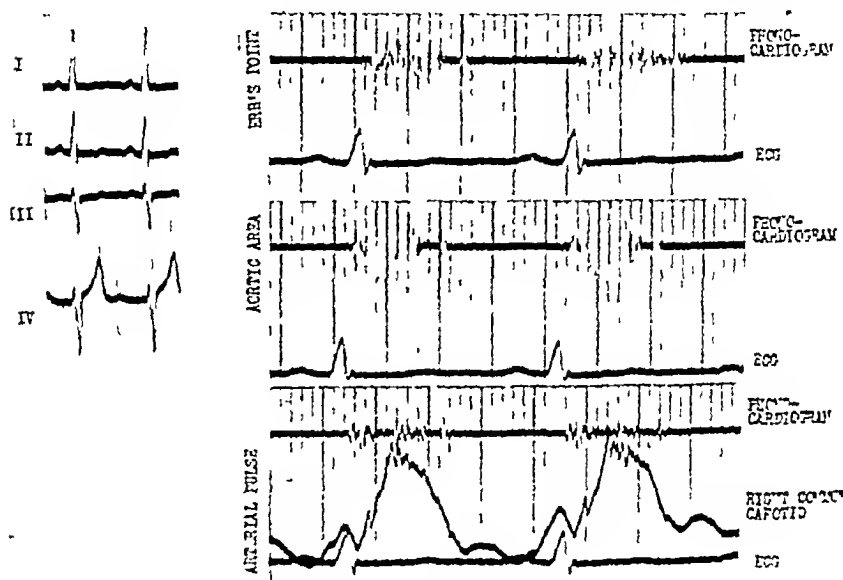


Fig 71 (Case II)—Aortic stenosis, dilated ascending arch, anomalies of the aortic arch. The electrocardiogram suggests left ventricular enlargement. Phonocardiographic records reveal a systolic murmur of highest amplitude over the aortic area. The second aortic sound is of diminished amplitude. A prolonged decrescendo diastolic murmur is best recorded over Erb's point. The carotid arterial pulse tracing shows a slow rise, an anacrotic notch and systolic vibrations.

tracing recorded over the right common carotid artery reveals a slow rise, an anacrotic notch and systolic vibration (Fig 71). Fluoroscopy shows considerable left ventricular hypertrophy and dilatation. The ascending aorta seems considerably dilated, showing dynamic systolic pulsations. This is even seen to a better advantage in a slight left anterior oblique view (Fig 72).

Angiocardiography reveals a marked dilatation of the ascending aorta. The aortic arch has an irregular outline with distinctly narrowed and sharply angular transition to the descending portion. The cervical arteries appear rather wide and somewhat tortuous (Fig 72).

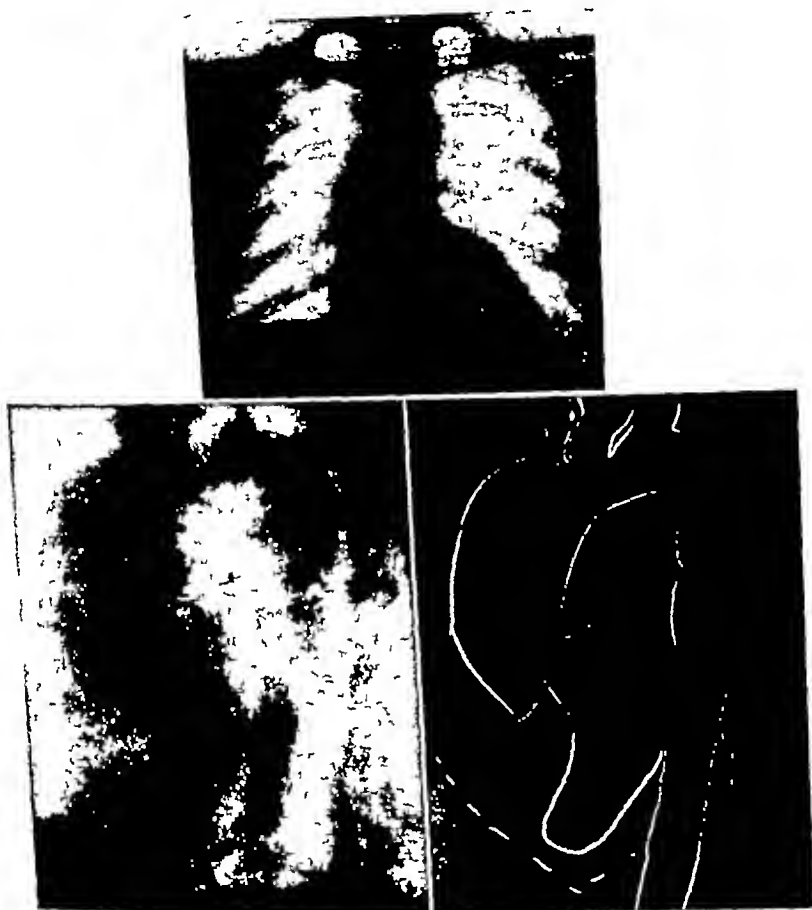


Fig 72 (Case II) —The left ventricle is hypertrophied and dilated. The ascending aorta is markedly dilated. The isthmus is sharply angulated and the descending aorta is irregularly narrowed.

Case III. Subaortic Stenosis. Peripheral Signs Ordinarily Considered Those of Aortic Valvular Stenosis

D L is a boy of 9. A cardiac murmur was discovered at the age of 6 months and the diagnosis of congenital heart disease was made. At 7 years of age this general diagnosis was confirmed by investigations at the Mayo Clinic. Several months ago the patient developed fever and weight loss leading to hospitalization elsewhere. Blood cultures were found positive for streptococcus viridans. Because of the presence of a systolic and diastolic murmur over the "base" the diagnosis of a patent ductus arteriosus with superimposed bacterial endarteritis was made. However, no ductus was found during a surgical exploration. The physical examination at the time of admission revealed a febrile, pale white boy with mild clubbing of his digits. The heart was enlarged to the left. A coarse systolic thrill was best felt over the aortic area, where also a loud systolic and diastolic murmur

was heard. The pulse was rapid and small, the blood pressure being 90/70 mm of mercury. The hemoglobin was 66 per cent and the blood cultures were positive for streptococcus viridans alpha. There were no other contributory positive findings. The patient died on the third day after admission.

The postmortem examination showed subaortic stenosis, subacute bacterial endocarditis of the aortic valve without diminution of the orifice, marked left ventricular hypertrophy, supraventricular mycotic aneurysm of the aorta, and acute fibrinous pericarditis. On opening the left ventricle the outflow tract appears markedly narrowed due to a circular white fibrous appearing tissue of about 1 cm in width extending to within 3 mm of the level of the aortic ring. Near the valve there is a ridge showing an elevation of about 3 mm. The diameter of the left ventricular outflow tract at the subaortic stenosed region is 7 mm.

Case IV. Subaortic Stenosis with Narrowed Aortic Isthmus

S F, a boy of 14½, has been asymptomatic throughout his life. Although from time to time the patient attends a cardiac clinic for routine examinations

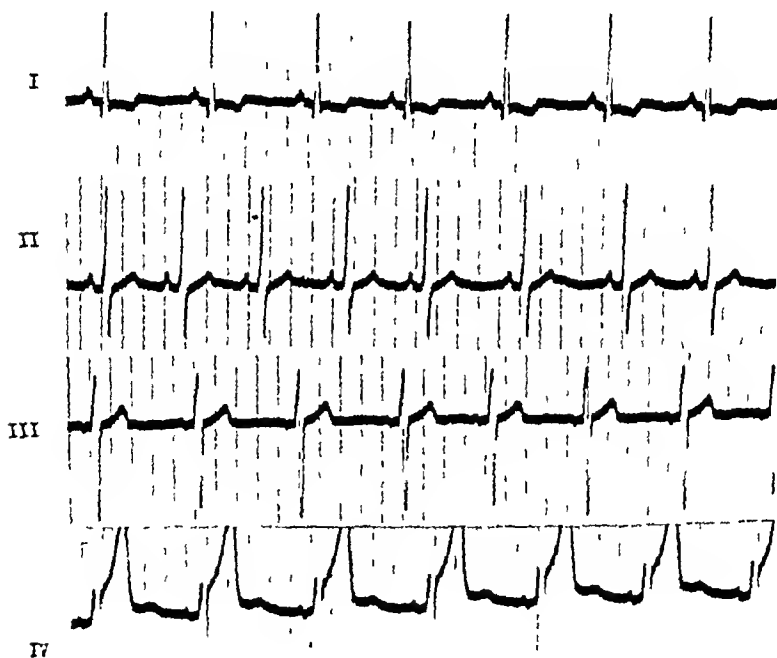


Fig 73 (Case IV) —Subaortic stenosis with narrowed aortic isthmus. The electrocardiogram shows evidence of marked left ventricular enlargement.

and has been advised to limit his physical activities, he actually engages in all available athletic activities. A cardiac murmur was discovered in early childhood

during a routine examination. In the clinic the diagnosis was considered to be interventricular septal defect.

On physical examination he shows considerable pallor which he considers his normal complexion. The heart is considerably enlarged to the left, the apical impulse being broadened and heaving. A coarse, vibratory systolic thrill is felt best over Erb's point and the cervical arteries. A loud systolic murmur is heard with maximal intensity over Erb's point, transmitted to the arteries of the neck. The aortic second sound is well heard and of normal intensity. Phonocardiograms confirm the auscultatory findings. The blood pressure was 94/72 mm.

A pulse tracing recorded over the right common carotid artery shows a very slow rise, an anacrotic notch, a systolic plateau and systolic vibrations.

The electrocardiogram reveals regular sinus rhythm, marked left axis deviation, QRS complexes of unusually high voltage. RST, 1 and 2, are slightly depressed, elevated in lead IV. T₁ is diphasic. The changes suggest marked left ventricular enlargement (Fig. 73).

Fluoroscopy and conventional radiographic examination revealed considerable cardiac enlargement, particularly to the left and slightly to the right. The left ventricular pulsations appeared rather sluggish. Angiocardiographic examination shows the aortic valve to be apparently normal. Below it there is a persistently visualized ridge. The transition of the aortic arch into the thoracic aorta is sharply angular, the isthmus itself being narrowed.

Case V. Aortic Stenosis. Anomaly of Aorta. Cerebral Dysfunction

M. S., a girl of 17, had a cardiac murmur discovered during infancy. The girl remained asymptomatic until about five years ago when she noticed mild dyspnea on exertion, frequent attacks of migraine-like headaches and occasional fainting spells. During the past year she experienced almost weekly attacks of blurred vision, double vision, bilateral temporal headaches with scotoma. Frequent fainting spells without convulsions or incontinence and attacks of epigastric pain and lower sternal pressure occurred, accompanied by nausea. She has been attending a cardiac clinic since earliest childhood.

Physical examination reveals the patient to be of normal complexion and body build. There is no apparent cardiac enlargement. A coarse vibratory thrill is felt over the aortic area, Erb's point and carotid arteries. A loud, harsh, systolic murmur is best heard over the aortic area and transmitted to the arteries of the neck. The second aortic sound is of increased intensity and closely followed by a faint prolonged diastolic murmur which is best heard over the midsternum. These auscultatory findings are confirmed by phonocardiography.

An arterial pulse tracing recorded over the right common carotid artery reveals a very slow rise, an anacrotic notch, a plateau and systolic vibrations. The blood pressure was 90/70 mm.

Electroencephalographic examination reveals a moderate amount of symmetrical and diffuse 3-8 per second activity without focal accentuation. These changes were considered to indicate a diffuse cerebral dysfunction similar to that seen in a variety of conditions such as cerebral anoxemia, hypoglycemia, toxic and metabolic disorders. No evidence of a focal lesion or an idiopathic epilepsy was found. During the administration of oxygen the record showed a diminution in the degree of abnormality. It was also noted that the nausea of which the patient complained during the recording was promptly relieved by the oxygen.

Fluoroscopy and conventional radiographic examination shows no evidence of chamber enlargement. The ascending aorta is markedly dilated, showing dynamic systolic pulsations (Fig. 74).

Angiocardiographic examination shows a marked dilatation of the ascending

aorta and the aortic arch. The transition to the thoracic aorta is sharply angular (Fig 74)

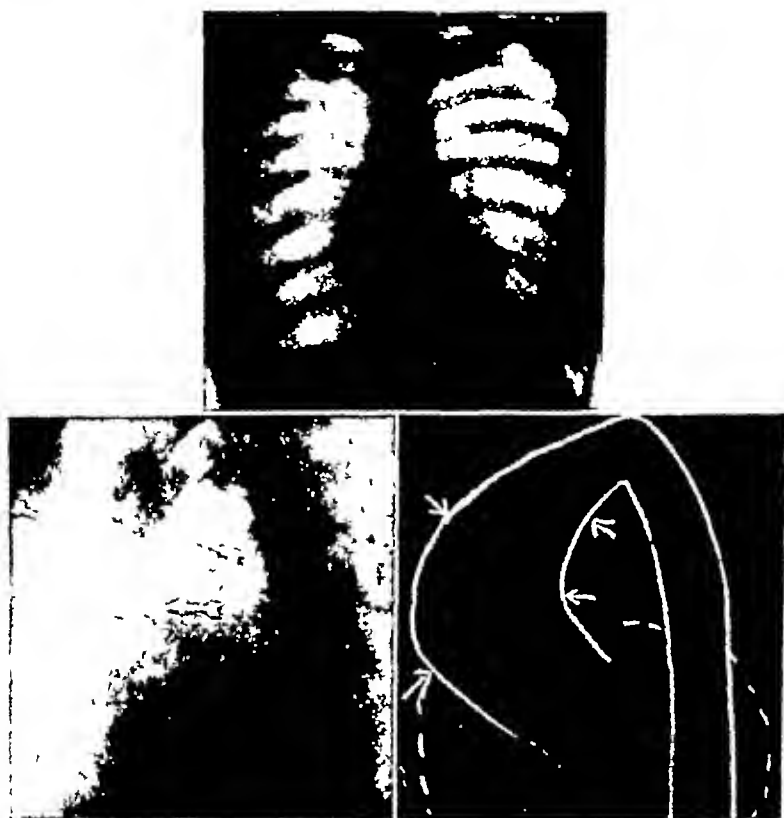


Fig 74 (Case V)—Aortic stenosis, anomaly of aorta. The ascending aorta is markedly dilated. The isthmus shows a sharply angular deformity.

Case VI. Aortic Stenosis Coarctation of the Aorta

T. W. is a boy of 5. The patient's birth and early development has been perfectly normal. There is no history of cyanosis, dyspnea, etc. In February, 1910 he contracted measles at which time his physician discovered a loud systolic murmur over the aortic area. The parents had never been told previously that the child had a murmur.

Physical examination reveals a well developed boy of healthy complexion. There is no apparent cardiac enlargement. An intense systolic thrill is felt over the aortic area and over the arteries of the neck. The pulsations in the lower extremities, femoral, popliteal, posterior tibial and dorsalis pedis, are felt with the greatest difficulty. On the other hand, faint but definite arterial pulsations are felt over both scapular and upper intercostal spaces posteriorly. A loud, coarse systolic murmur is best heard over the aortic area and over the carotid arteries. The second aortic sound is of normal intensity. These auscultatory findings are

confirmed by phonocardiographic examination. Arterial pulse tracings recorded over the carotid arteries show an anacrotic notch, systolic plateau and systolic vibrations (Fig 75). Simultaneous pulse tracings recorded over left radial and

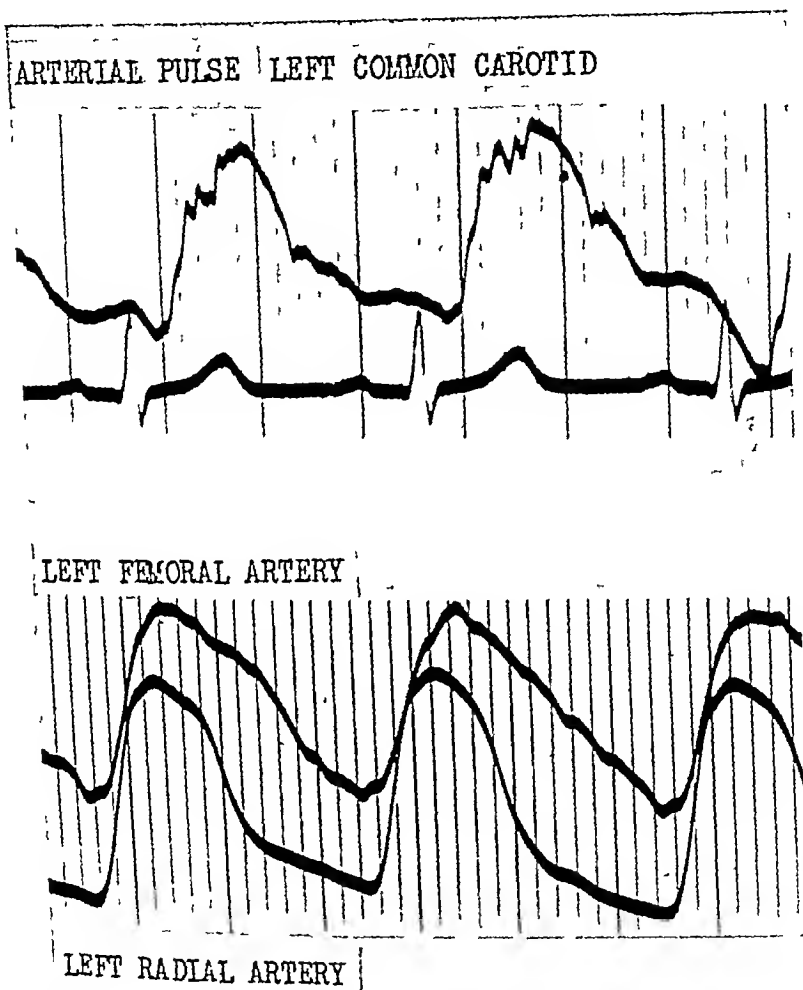


Fig 75 (Case VI) —Aortic stenosis, coarctation of the aorta. The anacrotic notch, the slow rise, systolic vibrations and plateau recorded in the arterial pulse tracing indicate obstruction to the left ventricular outflow tract (aortic or sub-aortic stenosis). Simultaneously recorded left radial and left femoral arterial pulse tracings reveal the radial pulse precedes the femoral pulse by 0.03 seconds. This is characteristically found in coarctation of the aorta.

left femoral arteries reveal the radial pulse to precede the femoral pulse by 0.03 seconds. (Normally the femoral pulse precedes the radial pulse 0.04 to 0.08 seconds [Fig 75]). Blood pressure readings were 112/68 in the left arm and 114/72

above 1.25 mg per 100 cc (whole blood) Davidson¹ reported that the average serum bilirubin level was about 5 mg. However, some infants showed clinical icterus with a serum bilirubin of 2 mg, while others failed to become icteric at 10 to 12 mg. Waugh,³ Hirsch² and Ross⁵ similarly found that 5 mg per 100 cc represented the level at which icterus was first manifest. Larsen and With⁶ found the threshold to be approximately 9 mg per 100 cc. This variation in threshold is in part due to differences in technics employed by the various investigators and in part to the difficulty in determining early icterus in the newborn. Larsen and With⁶ point out the great discrepancy between the adult threshold and that of the newborn infant, the adult developing jaundice when the bilirubin rises over 2.5 mg per 100 cc. The explanation for this difference is not clear nor is the explanation for the variation in the threshold in infants apparent. Several writers attribute such variation to differences in the skin and elastic tissue of infants.

The erythema characteristically present in the skin of the newborn infant renders difficult the detection of faint icterus. Icterus may first become apparent in the palate and then the skin and sclerae, although the edema of the eyelids present in most newborn infants usually prevents the early detection of scleral icterus. Smith⁷ points out the value of pressure by the finger or by a glass slide in reducing the erythema of the skin, thus making manifest the presence of faint icterus.

Numerous theories have been suggested to account for physiological jaundice or icterus neonatorum. The most widely accepted theory is that the polycythemia present in the fetus as a result of the relative state of anoxia during intrauterine life is no longer required following delivery when aeration of the infant's lungs makes oxygenation of the blood an efficient process. Hence, the excess red cells are destroyed, giving rise to an excess of bilirubin. Since no correlation has been found to exist between the degree of reduction of the red blood count and the hyperbilirubinemia,⁵ an additional explanation is necessary to account for the jaundice. This has been explained by the immaturity of the liver of the newborn infant, resulting in its failure to excrete bilirubin to a degree sufficient to maintain a normal serum bilirubin. In favor of this hypothesis is the higher incidence of jaundice in premature infants whose livers, less mature than those of full term infants, function even less efficiently.

Although the above theories may account for the development of physiological jaundice, they do not explain the presence of an elevated serum bilirubin at the time of birth, assuming that the stimulus to destruction of red blood cells is the spontaneous respirations of the newborn. The elevation of serum bilirubin at birth cannot be due to overproduction by the mother inasmuch as the mother's serum bilirubin at the time of delivery is normal. Several writers subscribe to

the following theory proposed by Schick⁸ to account for the elevated serum bilirubin at birth. Hemoglobin released by the destruction of maternal blood in the placenta is made available to the fetus, thus increasing the infant's bilirubin. This hypothesis has little factual evidence to support it, however, up to the present time, no other satisfactory explanation for the elevated serum bilirubin at birth has been proposed.

If the above theories are accepted as the logical basis for the presence of an elevated serum bilirubin at birth and the development of physiological jaundice, then the conclusion may be drawn that physiological jaundice is extremely unlikely at birth but will make its appearance some time *after* the birth of the infant. Consequently, one may also conclude that jaundice at birth is the result of hemolysis of red blood cells due to a pathological process existing prior to delivery (as in erythroblastosis fetalis) or to an abnormality or disease within the liver.

CASE PRESENTATIONS

Case I Congenital Atresia of the Bile Ducts

B.R.G. the fourth child of healthy parents, whose siblings had a normal past history was born at term following a short, uncomplicated labor. Faint jaundice was visible at birth and the placenta and vernix were said to be normal. The infant, mother and father were Rh-negative. The liver was felt 2 fingerbreadths below the costal margin and the spleen 1 fingerbreadth. The infant's red count was 5.8 million, hemoglobin 17 gm., and there were 2 normoblasts per 100 white blood cells. The cord blood Wassermann test was negative, x ray of the long bones showed no abnormalities.

The infant nursed well and appeared normal except for the icterus which gradually increased. Frequent blood counts continued to show normal hemoglobin and red count. The liver became somewhat larger but the spleen was no longer palpable on the third day of life. Normal meconium stools were passed but on the fifth day of life the stools appeared grayish white in color. Serum bilirubin on the ninth day of life was 10 mg. per 100 cc. the van den Bergh reaction was immediate direct, and bile was present in the urine. No bile pigments were demonstrable in the stools which continued to be light in color, and the serum bilirubin slowly but steadily rose until on the thirtieth day of life it had attained a level of 20 mg. per 100 cc. The liver on this day was palpable about 4 fingerbreadths below the costal margin and the spleen which had enlarged again was down about 2 fingerbreadths.

An exploratory laparotomy was performed on the forty-four day of life revealing atresia of the hepatic and common bile ducts. Following operation the infant developed a pneumonia which failed to respond to sulfadiazine and penicillin therapy and death occurred on the fifth postoperative day.

Holmes⁹ in 1916 reviewed over 100 infants with biliary tract abnormalities and reported that none of these patients had jaundice at birth. He stated that the icterus became visible in from two to five days. Since the publication of his paper, several authors have pointed out that jaundice may be present at birth in infants with congenital

atresia of the bile ducts ^{10, 11, 12, 18} Jaundice may not appear in patients with congenital atresia until two or three weeks after birth According to Baker,¹⁴ patients with onset of jaundice after the second week of life are rare Because of the number of patients with jaundice beginning between the fifth and fourteenth day of life, the suggestion has been made that the jaundice due to biliary atresia begins relatively late in all patients and that the icterus of early origin is due to physiological jaundice

As the jaundice increases in intensity, it changes from the golden yellow color characteristic of physiological icterus to a greenish-yellow color This may be noted at any time from 1 to 3 months of age, depending on the rapidity of the rise of serum bilirubin Ladd and Gross¹¹ stress the fact that once jaundice appears the intensity of the color never decreases

The liver may be enlarged at birth but, in the majority of patients with congenital atresia of the bile ducts, the liver is normal in size at birth and very gradually enlarges, frequently reaching the level of the umbilicus and becoming quite firm The spleen similarly may be enlarged at birth but is usually not palpable As the jaundice deepens, the spleen becomes palpable and gradually increases in size

The meconium of infants with congenital atresia of the bile ducts may have a normal green color Meconium begins to be formed about the fourth month of intrauterine life and will be bile-stained, provided the blocking of the biliary tract does not become complete before the fourth month Whether or not the meconium appears normal, the stools in patients with atresia quickly become white or clay-colored and greasy As the jaundice increases, the stools occasionally appear slightly yellow This may be due to admixture of the deeply colored urine with the stool or to the secretion of bile by the intestinal mucosa which is intensely stained with pigment In such instances, the bile may have stained only the outer surface of the stool and examination of the inner portions will reveal the absence of bile pigment

The urine becomes dark shortly before icterus appears and persistently reveals increased bilirubin Traces of urobilinogen may be detected early in the disease but this soon disappears from the urine Accurate determinations of urine bilirubin and urine and stool urobilinogen by the newer methods have not been reported in such patients Further work along these lines may permit the earlier diagnosis of congenital atresia of the bile ducts

II. Temporary or Intermittent Obstruction of the Bile Ducts

J L, the first-born of healthy parents, was delivered normally at term Jaundice was present at birth and the first urine voided was very dark and gave a positive test for bile The placenta and vernix were normal in appearance The liver was not enlarged and the spleen was not palpable The infant's blood was Rh-

negative and blood counts shortly after birth and at subsequent intervals revealed no anemia. The mother's serological test for syphilis was negative. The infant's serum bilirubin six hours after delivery was 3.5 mg per 100 cc., on the fourth day 6 mg., tenth day 7 mg., sixteenth day 10 mg., twenty-third day 12 mg., twenty-fifth day 8 mg., thirty-fifth day 6.2 mg., and on the forty-second day 10 mg per 100 cc. On the eighth day of life the liver was palpable about 2 fingerbreadths below the costal margin and the tip of the spleen was palpable. The infant's meconium appeared normal in color. Urine tested by the methylene blue technic¹⁸ showed marked variations in bilirubin from day to day. The stools which became light in color during the first week of life, gave negative tests for bile pigment but on several occasions were normal in color and were positive for bile. Throughout the infant's course he appeared in good health and gained weight. The fluctuations in serum and urine bilirubin, together with the occasional appearance of bile pigment in the stools, led to the diagnosis of obstruction of the bile ducts, perhaps by inspissated bile. A duodenal tube was passed and 20 per cent magnesium sulfate was injected into the duodenum on three consecutive days. Following this procedure, or coincidental with it, the infant's icterus gradually faded, the liver returned to normal size and the stools appeared normal in color. The serum bilirubin reached 1 mg per 100 cc. on the sixty-third day of life.

Temporary or intermittent obstruction of the bile ducts by mucus or inspissated bile gives rise to a clinical picture which usually simulates that of congenital atresia of the biliary tract. When such obstruction is complete, it is impossible to distinguish the condition from congenital atresia. However, in infants with fluctuating levels of serum bilirubin, together with the intermittent appearance of bile throughout the stool, the diagnosis of temporary obstruction by mucus or bile should be considered. Several infants reported in the literature whose jaundice disappeared despite the diagnosis of inoperable atresia of the bile ducts had, in all likelihood, mucus or bile obstruction of the bile ducts. Snelling¹⁶ has recommended the administration of milk of magnesia and bile salts with feedings, together with the administration of magnesium sulfate by duodenal tube, to patients whose obstruction may be due to inspissated bile or mucus.

Case III. Congenital Syphilis

J F, a first-born, was delivered at term following a short labor. He was admitted to the hospital approximately four hours after birth because of jaundice present at the time of delivery. The birth weight was 6 pounds, 2 ounces and the infant did not appear ill. Definite icterus of the skin and mucous membranes was present. The vernix and placenta were reported to be normal by the attending physician. The infant's liver was $2\frac{1}{2}$ fingerbreadths below the costal margin and the spleen was enlarged to about 1 fingerbreadth. The remainder of the physical examination was negative save for mild, pitting edema of the lower extremities. Serum bilirubin obtained shortly after admission to the hospital, was 4 mg per 100 cc. with a biphasic van den Bergh reaction. The infant's red blood count was 5 million, the hemoglobin 15 gm. and the smear revealed 3 nucleated red blood cells per 100 white cells. The infant's and mother's blood factors were Rh-positive. Blood cultures were negative. The meconium and stools which were subsequently passed were normal in color. X rays of the infant's long bones revealed a marked osteochondritis and the infant's Wassermann and Kahn tests were

positive. The mother's serological tests for syphilis likewise proved to be positive, the mother denied having received any antiluetic therapy. The infant was started on penicillin therapy and sixteen days after the onset of treatment the jaundice had disappeared. At 3 months of age, the liver and spleen no longer were enlarged.

Although most discussions of jaundice occurring during the neonatal period include congenital syphilis in the differential diagnosis, frank jaundice in the course of congenital syphilis occurs infrequently. Certainly, icterus at birth due to congenital syphilis is most unusual. Congenital syphilis with jaundice may simulate erythroblastosis fetalis, with enlargement of the liver and spleen and with anemia. However, other stigmata of syphilis assist in making the correct diagnosis inasmuch as these infants have a severe infection. In such infants, a well developed osteochondritis is usually present and frequently a periostitis. The mother's serological test for syphilis is, of course, of chief importance in the diagnosis.

The edema which is present in some of the patients with congenital syphilis is probably due to the diffuse hepatitis which results in a marked lowering of the serum protein with reversal of the albumin-globulin ratio.

DISCUSSION

Three patients have been presented to illustrate a few of the problems concerning jaundice noted at birth. Although the presence of an elevated serum bilirubin at birth in most infants makes possible the "physiological" appearance of jaundice at birth, the possibility seems to be remote, on theoretical grounds all instances of jaundice noted at the time of delivery may therefore be considered pathological in origin.

Halbrecht¹⁷ has designated jaundice which appears in the first twenty-four hours after birth as icterus neonatorum precox and differentiates this type from physiological jaundice which he believes makes its appearance later. He contends that this early type of jaundice is due to the passage of isohemagglutinins anti-A and anti-B from the mother to the infant where they hemolyze the infant's red cells and produce an increase of bilirubin. Such a mechanism could give rise to jaundice present at birth since the pathological hemolysis of red cells may occur in the fetus prior to delivery, the situation being similar to that found in erythroblastosis fetalis.

The need for further studies of the Rh factors, the Hr factors and incompatibility in the A and B blood groups in patients with jaundice at birth is obvious. In view of the fact that some patients with congenital atresia of the biliary tract may have jaundice at birth while others may show initial jaundice two to three weeks after delivery, it is possible that the early jaundice is due to factors other than the jaundice per se. This may similarly be true of other diseases apparently responsible for jaundice present at birth.

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TREATMENT OF TOXEMIA OF PREGNANCY

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THIS paper considers certain aspects of the treatment of preeclampsia and eclampsia as defined in the American Classification of Hypertensive-Albuminuric Pregnancy (Group B), whether or not superimposed on essential hypertension or the nephropathies (Group A).

In 1937¹ and in 1945² I reviewed more broadly the problem of toxemia of pregnancy, attempting to bring our knowledge up to date within space limitations.

A large portion of this material, which was unpublished till now, was presented as part of the "Walter Channing Day" program (1946) before the alumni of the Boston Lying-in Hospital. My talk was preceded by a discussion by the Smiths on their concept of the endocrinological etiology of eclampsia (George Van S Smith) and prophylactic treatment with stilbestrol and treatment of the established condition with the "antitoxin" substance called at the moment PPs (protective pseudoglobulin factor) (O W Smith).

For completeness they have kindly supplied the following brief summary of their talk, together with six recent references—three published, one soon to be published and two to be published in the future ^{3, 4, 5, 6, 7, 8}

PROTECTIVE PSEUDOGLOBULIN

"Since 1933, when Smith and Smith first published results on a difference between normal and toxemic pregnancy as regards the amounts of gonadotropic and estrogenic hormones in the blood and urine, these investigators have continued their studies of hormone levels in pregnant and nonpregnant women and have, furthermore, gained evidence for the presence of a toxin in the circulating blood of women during menstruation, labor and late pregnancy toxemia. The formation or release of this toxin in these situations appears to be dependent upon withdrawal of hormonal support from endometrium and decidua. The analogies between these three processes have led to the concept that a menstrual-like phenomenon is involved in labor and that toxemia results from changes entirely similar to those which normally occur at term, the difference being that the products of conception and the source of the toxin are retained. According to this concept, therefore, the signs and symptoms of preeclamptic toxemia

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are directly referable to the presence of a toxin in the circulating blood, its formation being associated with withdrawal of estrogen and progesterone"

"The Smiths have shown that the premature withdrawal of estrogen and progesterone which characterizes late pregnancy accidents may be prevented by diethylstilbestrol, the mechanism of this effect being increased utilization of chorionic gonadotropin for the placental elaboration of these steroid hormones. For the definitive treatment of pre-eclamptic toxemia, they have recently been working with a factor protective against the toxin which they have found in the pseudoglobulin fraction of fluids associated with tissue damage. This factor they term protective pseudoglobulin, or PPs. In six therapeutic trials upon patients who had already been under a routine toxemia regimen for one to three weeks, administration of PPs was followed by a marked decrease in albuminuria, a drop in blood pressure, particularly the diastolic, and a loss of weight. In four of these patients this effect was maintained for as long as injections were continued, whereas omission of therapy resulted in recrudescence of toxic signs. In two of the more severe cases the initial improvement was not maintained by continued injections but in one of these the administration of twice as much PPs again brought toxic signs under control. The effect of diethylstilbestrol upon patients already showing toxic signs was also investigated. It was concluded that the presence of toxin prevented this compound from stimulating the placental secretion of steroid hormones. The value of this drug in late pregnancy toxemia is, therefore, limited to its use as a preventive measure, whereas PPs, when certain difficulties in its preparation shall have been overcome, promises to be a valuable aid in definite therapy."

I am incompetent to criticize the Smiths' work. Whatever one concludes in respect to treatment from their limited amount of material, their studies have served to demonstrate the absolute necessity for daily *quantitative* determinations of the urinary albumin in following the course of a preeclampsia (a point I have emphasized for ten years) for purposes of prognosis and for determining the optimum time for interruption of pregnancy. Moreover, they have devised a simple method for this determination."

A CONCEPTION OF MANAGEMENT

My conception of treatment of hypertensive-albuminuric pregnancy in no way differs from that of others—at least theoretically. It dates back to the years just after World War I when Dr. Burton Hamilton, with fresh ideas on heart disease acquired from MacKenzie, began his truly outstanding contributions to an understanding of the heart in pregnancy at the Boston Lying-in Hospital, the results of which

* Space does not permit the detailed method but it may be published soon

were his textbook⁹ and a highly satisfactory reduction in cardiac mortality in the clinic and in the private work of our staff. This mortality reduction was largely brought about by the decline in use of hysterotomy in cardinals. Whatever else the various manifestations and behaviors of hypertensive-albuminuric pregnancy have behind them they are all essentially vascular although they develop at different rates of speed. With Dr. Hamilton, and based on his ideas, I wrote several papers on what, for lack of a better term, we called "Recurrent Toxemia." We showed that some success could be obtained in potential toxemias by the same routine of observation and precautions he had developed for actual cardinals. This was long before we had even a partially satisfactory classification of hypertensive-albuminuric pregnancy. What is said here represents the refinement and crystallization of this idea through the last twenty-odd years.

In 1944 Eastman and Steptoe¹⁰ analyzed 2418 cases of preeclampsia seen at Johns Hopkins Hospital from January 1, 1924 to December 31, 1943 in an effort to determine the causes of "toxemic failures." They state that "the wide variety of causes responsible for these failures illustrates so clearly the *everlasting vigilance* and *wary alacrity* necessary if preeclampsia is to be managed successfully."

As time has passed and the tentative classification has clarified the individual case and a variety of treatments of *established* toxemic conditions has been observed, I have become more and more impressed with the fact that established conditions in eclampsism do not yield to any available treatment other than that of emptying the uterus. This procedure loses babies—depending on their gestational age, the method of interruption of the pregnancy, whether or not the patient has eclampsism or toxic separation, or both, and hence is "toxemic failure." A given patient's condition for interruption can be improved greatly in a variety of ways, but these are not cures. In eclampsia we can control convulsions by several methods—with the veratrine regimen, perhaps more slowly and safely with magnesium sulfate intravenously although we do not yet know, perhaps by other methods—and so are able to empty the uterus with the patient a preeclamptic instead of an eclamptic, with more safety for the mothers and, at times, more for the babies. In severe preeclampsia, the same methods produce the same improved results.

If these observations are true the answer to our problem lies in preventing in so far as possible the development of these established conditions in every patient. The Smiths' endocrinological work shows many instances a six to eight weeks' lag between imbalance of hormonal curves and the appearance of clinical symptoms. It is my belief, and apparently theirs—on the basis of their advocacy of stilbestrol from the beginning of pregnancy—that whatever the clinical approach, it should be applied long before the appearance of this

unbalance. I understand that soon a reasonably large number of normal pregnant women will be "stilbestrol conducted" throughout pregnancy with a control group. This should throw some light on "stilbestrol toxemia prophylaxis."

THE "SUSPECT TOXEMIA GROUP"

In cardio disease the carefully made diagnosis by well established methods permits the immediate segregation of this group for extraordinary observation and precautions throughout pregnancy. Although every pregnant woman is potentially a candidate for toxemia of pregnancy it is not possible practically to give all the same extraordinary observation and precautions as applied to the known cardiac, nor is it practical for all patients to subject themselves to this. It, therefore, is imperative for us to select to the best of our ability a "suspect toxemia group" and labor over them faithfully and persuade them (often by fear) to take the ordered care proper for a potential toxicemic. Not all this "suspect group" will develop toxemia, but two results appear to come from this system in my experience, (1) many babies will be salvaged, and (2) many women who might have developed toxemia either by historical right or on suspicion will not so develop it. If I have a criticism of the obstetrician in general it is only that this selected group is, on the basis of review of case experience, too small, or to put it another way, I have seen many established toxemias in which one of two things appeared true in retrospect, either the patient should have been "suspect" and hence had special care and precautions, or prenatal care had been inadequate for good results, especially in regard to uncontrolled excessive weight gain. These cases are impressive not only in the clinic but in private practice.

Selection of Cases—A given patient should be placed in the "suspect group," with consequent special care, in the following conditions: established vascular disease, familial history of vascular disease, chronic glomerular nephritis, a history of acute nephritis, diabetes, history of scarlet fever, pyelitis-pyelonephritis in childhood or adult life, previous "pregnancy toxemia," history of stillbirth or premature delivery of a living child with or without toxicemic manifestations, a history of sterility or habitual abortion, obesity, low basal metabolism with or without high blood cholesterol, a diastolic pressure of 70 or more on two or three observations and a toxicemic appearance.

The importance of appearance is exemplified by Mrs. C. who had a toxic separation of the placenta with a Couvelaire uterus and a dead baby although there had been no manifestations of toxemia except a 4 pound weight gain in a week and slightest possible trace of albumin *once*, but whose appearance had so impressed me that I had immediately in her earlier pregnancy, subjected her to rigid precautions in spite of an otherwise negative physical examination. The first

pregnancy was uneventful but in the second the patient became careless of her prenatal care, with the above result. She is now pregnant again and her behavior is perfect

Importance of Rigid Management—Having placed a given patient in the "suspect toxemic group" on these grounds, a conference with husband and wife is called for, at which a written detailed routine for care is given them and the grave need for its observance is emphasized. If they have already had a dead baby as a result of toxemia it is easy to be convincing, if not, constant reiteration will be necessary at each visit. The routine for care is the same as for a pregnant patient with rheumatic heart disease, with which all are familiar. Again and again it has been demonstrated that the exact detailed observance of this routine spells the difference between success and failure. I have seen repeated examples of carelessness on the part of obstetrician, clinic or patient, or all, when reviewing an established toxemic condition. It is the obstetrician's duty to see that neither he nor the patient is careless, it is not the patient's business to ask for extra prenatal visits.

Points in Prenatal Care.—I would emphasize certain points in this extreme prenatal care for the suspect toxemia group.

Frequency of Contact Between Doctor and Patient—I consider visits every two weeks during the first sixteen weeks and weekly visits thereafter an essential part of this care. Urine specimens should be seen every week for the first sixteen weeks and twice a week or every other day thereafter. At each of the visits the weight gain, blood pressure and urine findings are discussed openly with the patient. She is checked on her amount of rest, carefulness about wet feet, cold extremities, emotional state. At each visit the height of the fundus is measured—preferably by a line on the patient's abdomen to the sides as well as the top. The patient is asked to replace this line with 2 per cent mecurochrome when it washes faint in order to gauge the growth or lack of growth of the baby. Hormonal studies are of help, pre-lumbodorsal splanchnicectomy blood pressure studies each two weeks, if available, may prove useful in following each case.

Weight Gain—Edema is frequently the first sign of impending toxemia. Unless the weight is charted weekly against a normally expected weekly gain, early detection of this important sign can easily be missed.

Mrs. D, aged 41, fearing the menopause and newly wed to a man 62, ap-
five months pregnant on March 21, 1946. Her diastolic pressure was 80 on
occasions, her weight 194½ pounds. Her appearance was against her. She
placed on a "suspect toxemia" regimen and her weight when she was delivered
a full term child on July 12, 1946 was 173½ pounds. There was no evidence
toxemia.

Mrs. T., a patient with toxemia symptoms of six weeks' duration, during her previous pregnancy had had a weight gain of 40 pounds uncontrolled and had lost a 8 pound 10 ounce baby. She began this pregnancy at 136 pounds. After careful management she was delivered at term, without any toxemia, on September 30, 1946 of an 8 pound, 5 ounce child. Her weight at the time of the child's birth was 186½ pounds.

Neither of these patients had anemia or any signs of avitaminosis. Both were heavily subsidized with vitamins and minerals.

Control of the Patient's Behavior—Thus of necessity depends on the circumstances of the patient.

Mrs. D. of the first case, runs a business in Boston commuting daily from a suburb. She worked each day from 9 to 5 until the eighth month of her pregnancy. Our office visits were at 8:30 A.M.

Mrs. T. lived in Saco, Maine. Her visits were necessarily curtailed but her husband watched her weight carefully. She is again pregnant and having learned how to take care of herself will be looked after locally.

Mrs. M., whose parents both died in their 50's of hypertensive disease, is the mother of three nontoxemic girls but essayed a boy against advice and gut him. She started her pregnancy with blood pressure of 140/90. She never left her comfortable estate after the sixteenth week and I saw her every Sunday morning at home from then until two weeks before term. This patient showed albuminuria and increased hypertension before delivery. Labor was induced, her blood pressure was stabilized at 180/110 and she is now a candidate for lumbodorsal splanchnicectomy.

We did the best we could with these three under different circumstances.

TREATMENT OF ESTABLISHED TOXEMIA

Regarding treatment of hypertensive-albuminuric pregnancy once the condition is established, there is little I can say that is not known. This ground was covered in my review of 1945.² Our results with the veratrine regimen and with magnesium sulfate intramuscularly were reviewed in this paper and a short consideration was given to the advisability of using in its stead 2 per cent magnesium sulfate intravenously as employed by Peters in convulsive states, in those cases in which there is a known hypertensive underlie, in order to avoid the risk of cerebral accident by so rapid alteration in blood pressure as is produced by veratrine. Recently Willson,¹¹ reporting on a series of veratrine treated cases, expresses the opinion that oliguria is more likely to take place with the use of veratrine than without its use. If this is true it is possibly on the basis of prolonged lowered blood pressure. It is apparent that the final place of veratrine in the treatment of eclampsia lies in the study of much additional data in spite of Bryant's report,¹² although my experience does not permit me to agree with Willson's conclusions. I believe it most valuable in selected

cases I have never been able to see the sense of *routine* treatment of eclampsism Our reported series was short

Elsewhere we have reported² a detailed account by Newell and Smithwick of the use of lumbodorsal splanchnicectomy in hypertensive-albuminuric pregnancy I have seen one case—a sterility patient who was said to have become pregnant by a miracle—operated on in the sixth month in a desperate effort to save the situation in a severe established toxemia based on an initial hypertension The operation was unavailing, the baby died in utero and was miscarried The patient's blood pressure is now stabilized at 140/90 so should a second miracle occur her prospects are reasonably good under exceptional care The operation was not in vain It was interesting to note how well the patient took the vicissitudes of this unpleasant operation because of her willingness to try to keep the baby *

I have noted² that from 1916 to 1945 eighteen of our clinic patients have died of toxic separation of the normally implanted placenta and some have had miraculous escapes An equal number died when the policy was cesarean section and when the policy was conservative delivery from below The former died of "toxemia" for the most part, more than one-half the latter died of hemorrhage, the blood failing to clot The production of this condition appears to be dependent on the time element Therefore, rapid emptying of the uterus by section probably has a place in certain of these cases The problem is to determine which ones Since every "toxic" is a possible candidate for separation, every waiting patient with this condition should be completely studied from all possible angles to determine as soon as possible that this blood state may be developing² Furthermore, there is evidence that this condition of the blood may develop in toxemia without separation I enlarged on this in detail in the last review² In a recent paper read in New York, I explained why I do not think this type of death is simply "shock death" Inhalation anesthesia is surely contraindicated in this condition, yet we have often used it.

VITAMIN E IN THE "SUSPECT TOXEMIC GROUP"

The employment of vitamin E is moot ground since vitamin E blood levels are not yet determinable in a practical way,^{24, 25} and it is usual to say that sufficient vitamin E is obtained in a well rounded diet Yet it is used by many clinicians in patients subject to habitual abortion Experimental evidence in animals is only negatively conclusive, i.e. every potential toxic is a candidate for placental separation since synthetic vitamin E in 300 mg doses a day has seemed to help, I have given it to all "suspect toxemia" patients

* More data, by Newell and Smithwick, on lumbodorsal splanchnicectomy both in preparation for pregnancy should soon be published

With the appearance of toxemic signs and symptoms in the suspect and non suspect group, since all are candidates for toxic separation, vitamins K and C and, if available, choline dihydrogen citrate, in addition to vitamin E, are indicated in an effort to meet this potential blood condition should the placenta separate, the use of these is based on immediate routine tests and signs and symptoms indicated in the 1945 review,² and the New York paper¹³

Three other aspects of the problem might well be investigated (1) The effect of alcohol on the "suspect toxemic group" I have presented a meager amount of evidence to show that it should be omitted from the dietary of these patients² (2) The effect of moderate smoking Is it a sedative rather than an excitant of hypertension in this group, if the patient smokes habitually? (3) The importance of semen examination in prospective "suspect toxemic" cases, with the advantages of beginning a pregnancy when the husband's semen is at its potential best

A review of Shute's work in the toxemias,^{14 15 16 17 18 19 20} which in my opinion should be either refuted or substantiated, but not ignored, shows that in prophylaxis we must reconcile at least three relatively modern trends of thought (1) The Smiths' postulate that stilbestrol alone is sufficient to prevent miscarriage, premature labor, placental degeneration and eclampsia and toxic separation They have not used vitamin E and the inference must be drawn that they consider it useless (2) My theory that vitamin E is harmless, protects placentation, and tends to protect the placenta against degeneration in all groups (A and B), superimposed or not, in the American Classification, that it is worth using in all potential toxemias of pregnancy on the basis of clinical experience and evidence that it "fosters the integrity of the capillary walls,"²¹ and that it is prophylactic against eclampsia and toxic separation of the placenta I fear massive doses of stilbestrol because of its water-retaining potentialities (denied by the Smiths) added to the water-retaining factor in toxemia I use stilbestrol in doses up to 15 to 20 mg daily and withdraw it slowly (3) Shute's completely worked-out program based on plus or minus estrogen assay, giving a clear-cut reason for using vitamin E in a certain group of cases and estrogens in the other group Surely this is a far simpler classification than any other if the estrogen plus or minus test is valid

It seems apparent that if we could reconcile these opinions we might make progress

Comments follow with the hope that they may contribute something to future understanding.

It appears that vitamin E when given continuously may act as a "chronic vasodilator" Its apparent success in intractable angina pectoris²² after other medication had failed to control pain supports this

claim Furthermore, its apparent value in various experimental and human purpuras²² suggests that it may have value as adjunct therapy in toxic separation of the placenta

That vitamin E seems to protect the placenta is suggested by the previously published details² of five pregnancies in two sisters with minimal toxemia in which complete placental studies are given I am able to report a sixth pregnancy in the two sisters This pregnancy occurred in the sister (H G) who lost her first baby in utero at thirty-five weeks, weight $1\frac{1}{2}$ pounds below expected gestational age, with a grossly and microscopically infarcted placenta of indaequate ratio The present pregnancy resulted in a normal placenta and a normal weight child delivered by induced labor at 38 to 39 weeks In the latter pregnancy the weight gain was held to 7 pounds, an adequate sperm picture was present at conception (unknown in previous pregnancy but probably not good from subsequent examinations), no alcohol was permitted, 15 mg of stilbestrol was given daily and withdrawn slowly from the thirty-fifth week, and 300 mg tocopherex was given each twenty-four hours throughout pregnancy Her pregnandiol excretion was followed throughout by the Smiths and once stood still at about the thirty-fourth week Experimentally she was given 100 mg of stilbestrol for one week. When this was withdrawn by me the patient suffered in vague ways, "she felt awful," she said This result may well be expected, I am informed, because of the abruptness of the massive dose It raised pregnandiol excretion 10 per cent and thus remained normal until delivery It is of some interest perhaps, that the patient who had been having preumbodorsal splanchuectomy tests every two weeks experimentally showed in the same thirty-fourth week her only deviation from normal Scientifically bombarded from two angles at the same time I took refuge in the fact that the patient had no visible signs of toxemia and the baby was the right size for its gestational age The patient was at this time being seen in my office twice a week

The results in this case may indeed be coincidental but at least we have six pregnancies in two sisters with carefully checked placentas and fetal weights, which invariably correlated. Three normal placentas and three normal sized babies resulted when 300 mg of tocopherex were administered throughout pregnancy no matter what else was used or what other conditions were changed One dead baby in utero and two babies (one of which died of cerebral hemorrhage following induction), all accompanied by markedly infarcted placentas in the mothers and weights 1 to $1\frac{1}{2}$ pound below that expected for their gestational age, were obtained when the patients did not have vitamin E therapy Moreover, in the other sister (F M) in her second pregnancy prolan-estrin ratios were followed from the eighteenth week These followed the predicted course of a patient going into premature labor, she was given 25 mg progesterone and 5 mg alpha estradiol ly for six weeks (for detailed chart of results, see previous publication)² In spite of hormonal changes effected by the therapy she had infarcted placenta and the baby when born at 36 to 37 weeks weighed 4 pounds 2 ounces, although the expected weight was 6 or 7 pounds as judged by her two subsequent normal pregnancies in which the mother took vitamin E throughout, and no hormones She

received no vitamin E in this pregnancy and her minimal "toxemia" was negligible, she showed specifically a slight rise in blood pressure, little weight gain, no edema and no albumin

There remains one point that needs elucidation Shute¹⁶ has recommended vitamin E as prophylaxis against premature separation of the normally implanted placenta Hertig and I^{2, 13} have attempted a classification of separation of the normally implanted placenta based on pathological studies of these placentas in which we attempt to show that all maternal mortality in these cases (with the exception of an occasional case of "traumatic separation") occurs in the "toxic group" I, too, have advised vitamin E as prophylaxis for toxic separation by using it in all "potential toxemias" Yet in our experience, toxic separation of the placenta occurs in what Shute would call "true toxemia of pregnancy," that is, in the potentially convulsive type, in his words "estrogen negative" and therefore to be estrogen treated ("antagonist to E") and not E treated I cite two patients in illustration of what I mean

*

Mrs C suffered separation of the placenta in her second pregnancy with almost no sign of toxemia (excessive weight gain for one week and slightest possible trace of albumin in a delayed specimen) but with a Couvelaire uterus on section on a dead baby On 300 mg of tocopherex and no stilbestrol and more careful prenatal care she has just been delivered at 37 to 38 weeks of a 7 pound 2 ounce boy by repeat hysterotomy without toxemia.

This case proves nothing because, as brought out in a question by Kosmak,²³ no one knows or has yet figured out what chance a previous toxic separation has of repeating. In reply to his question I said I had studied the literature with no answer, but I assumed that if one prevented the toxemia one minimized the chance of "toxic separation" One more personal case may bear upon this

Mrs S lost a baby with "toxemia" in a town in New Hampshire; the baby was stillborn at 8½ months She had toxemic signs and symptoms from 6½ months Her blood pressure was 110/80 when I first saw her at two months in her second pregnancy there was no albumin She was put on 150 mg of tocopherex daily She was delivered normally of an 8 pound normal child. Weight gain was 8 pounds throughout pregnancy and there were minimal but definite toxemic symptoms. When she was seen in her third pregnancy her weight was 124 pounds blood pressure 110/80 She was again put on 150 mg. of tocopherex daily Labor was induced two weeks before term for persistent albuminuria at which time her blood pressure was 160/100 weight 136 pounds Pathological report "Premature separation of placenta ischemic necrosis of villi" The baby weighed 6 pounds at term; bleeding and clotting times were normal, tourniquet test negative other tests were not made.

This would lead us to assume that vitamin E is not a sure prophylactic against toxic separation, placental degeneration or preeclampsia

SUMMARY

Patients in the "suspect toxemic group" may either be permitted a trial of pregnancy under exceptional care, knowing that if trouble comes an early emptying of the uterus will do no harm, or if essential hypertension is pronounced a lumbodorsal splanchnicectomy is indicated, after which pregnancy may be allowed to proceed. I expect evidence to appear soon that the latter procedure in early pregnancy may permit successful termination of an otherwise hopeless pregnancy.

EXAMPLE Mrs. M., the patient of an associate, delivered at 31 to 32 weeks a 2 $\frac{1}{2}$ pound, 9 ounce baby which survived. The placenta was grossly infarcted. She was followed in pregnancy and subsequently for nine months by a competent internist, a diagnosis of chronic glomerular nephritis was made with complete findings. At the end of nine months there was no evidence of this except the history. The obstetrician and internist advised against another pregnancy. Asked what I thought, I replied I did not know but believed they did not know either. There was nothing to lose, possibly something to gain. She became pregnant quickly, followed her service husband all over the country throughout the pregnancy, delivered at term in New York without any abnormal events in pregnancy or labor to the extent that, as far as I can ascertain, this placenta was not examined pathologically. Since then the patient has had a third normal pregnancy and normal child.

THE "NONSUSPECT GROUP"

The importance of vigilance in the "nonsuspect group" of pregnant patients is exemplified in the following report of one of my own cases.

A primiparous patient suffered a cold with a sore throat and was put to bed, thus making impossible her regular two weeks' interval visit to my office. A mailed specimen of urine was too small in amount to test. When the patient later appeared at the office, seventeen days after her previous visit, she presented the alarming picture of a 10 pound gain in weight, 24 gm per 100 cc of albumin in the urine (previously none) and blood pressure of 160/100 (previously 90/50).

She was hospitalized and treated with PPs (O. W. Smith) for four days. Her albumin fell to 6 gm and she lost 5 pounds of her edema but her diastolic pressure began to rise. A cesarean section, under spinal anesthesia, was carried out—fortunately the patient was three weeks from term—and a 6 pound, 5 ounce child delivered which did well.

The respiratory infection might have happened six to eight weeks from term, with loss of the baby. The placenta showed a definite but slight area of separation. The separation could well have been complete and the mother also lost. One may speculate in view of the condition of the placenta whether the time spent in treatment to improve operative condition, which indeed it did, was judicious. In any event, we were fortunate. Of course, with the appearance of the infection of the respiratory tract the patient should have been followed aggressively.

CONCLUSION

There is a need for more rigid application of the well known principles of management in "suspect toxemia" patients. Physicians are urged not to depend too much on the magic of the endocrines and anti-toxin, which may offer great promise for the future, but when necessary are often an admission of failure to have prevented their need. In the "nonsuspect group" any untoward event, such as a respiratory infection, should be of immediate concern.

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OFFICE APPROACH TO THE PSYCHONEUROSES

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INTRODUCTION

THE magnitude of the problem of personality maladjustment has received emphasis during and since the recent war in both lay and professional publications. Statistical exactness concerning the number of people suffering from psychoneurotic illness (including psychosomatic disturbances) is not as yet possible. Weiss and English¹ estimate that at least two thirds of all patients present themselves with no or inadequate "organic" pathology to account for their complaints. Cobb² estimates that 2,500,000 psychoneurotics exist in the community and adds that this figure "is doubtless far too small even for those medically treated." He specifically separates from this group alcoholics (1,600,000) and stammerers (1,200,000), although there is excellent reason for believing that these individuals suffer from personality disturbances that are of importance in the genesis, perpetuation and treatment of their disorders. However inexact, these estimates serve to illustrate the tremendous proportions of the problem of psychoneurotic illness and to buttress the common and possibly over-conservative statement that "about 50 per cent of the patients who consult the general practitioner have complaints for which there is no discoverable physical or organic cause."³

From these figures the obvious conclusion is that the majority of these patients must be treated, if they are to receive any treatment, by the general physician, for it is manifestly impossible for the 5000 (approximately) physicians who have had special training in psychotherapy to meet the demand. Hence, the general physician must learn a technic of approaching personality problems that will enable him to feel reasonably secure, that will be safe for his patients and that will show good results.

Fortified with such a technic, the physician should be able to avoid some of the common pitfalls that have, and continue to, beset many in their dealings with psychoneurotics. For example

- 1 "Diagnostic treatment" or the making of repeated examinations in

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search of the elusive "organic" cause As one patient put it "I have had twenty-four years of diagnostic treatment from many doctors It has done me no good I'd like to get some real treatment for a change, so that I can feel better."

2 Being misled, by exclusion, into making a faulty diagnosis on the basis of an incidental and probably symptomatic finding such as "low blood pressure" or "chronic brucellosis" when the positive evidences of personality maladjustment are readily apparent but completely overlooked

3 Insulting a patient's intelligence by telling him that there is "nothing wrong," as no "organic" disease exists, that he merely "imagines" he is ill and that, if he wanted to, he could "buck up" or "snap out of it" Obviously, as many patients have pointed out, they would have "snapped out of it" long ago, if they could have, and would never have asked a physician for help

4 The production of "iatrogenic disorders" by the misinterpretation of somatic concomitants of anxiety as evidence of "heart disease" and the like, which may not be explicitly stated to the patient, but which he is capable of grasping from the physician's attitude or from the type of medication prescribed

TECHNIC OF INTERVIEWING

Basic in all therapy is knowledge of the condition that requires treatment Hence, the one most important tool the physician must possess is a technic that will enable him to obtain the facts that he must deal with, for unless these are forthcoming he is impotent, regardless of his theoretical command of psychopathology Certain specialized projective technic such as the Rorschach test and the thematic apperception test, and investigative-therapeutic procedures such as formal psychoanalysis, narcoanalysis and hypnoanalysis, are not available to or within the sphere of competence of most medical men Hence, physicians generally must rely upon straight-forward, verbal communication with their patients

Let the Patient Talk.—This is the most important single "procedure" the physician can master Too frequently the latter's "urge to do something" forces him to interrupt the patient's account of himself in order to get him back to the matter in hand Usually this attitude of impatience and of frustration simply leads away from "the matter in hand"—the patient as a total personality, not as the bearer of this or that recalcitrant organ Many emotionally disturbed people have a strong drive to talk out their troubles. Given half a chance by a sympathetically attentive and intelligently listening doctor, they disclose in full detail the important molding influences in their development and will adumbrate the place of their complaints in the total picture

The doctor's first task, then, is to encourage the patient to tell his story and to encourage himself to listen carefully. When a patient finds difficulty in starting, the doctor can help him by suggesting that he describe his complaints and their development as completely as possible. Should the patient bog down temporarily, he can generally be started again by simple questions like "What else did you feel?" "What had been going on before this?" "Who was with you?" If possible, the doctor can rephrase as a question a point the patient has just made, thus stimulating the patient to further elaboration. The process of elaborating upon the details of his complaints sets off further association chains which eventually bring out the meaning of the illness.

Special Points to Note.—While the patient tells his story the doctor watches carefully for the emergence of significant reactions. This task is facilitated by having certain key points in mind.

Reaction of the Patient During the Interview.—Careful yet unobtrusive observation of the patient can be cultivated so that the doctor becomes accustomed to detecting changes in voice, in general tension, in mood and similar differences, and to linking such changes with the material produced at the time.

Relations of the Patient with His Parents or Parent Substitutes.—Even cursory observation of children clearly demonstrates the importance of the individual's parents as molding influences in his personality development. Hence, the patient's account of his relations with his parents deserves close scrutiny. That this can scarcely be emphasized too strongly becomes increasingly evident during succeeding interviews.

Relations of the Patient with His Siblings.—This is a direct corollary of the preceding paragraph and embraces the concept of "sibling rivalry" in all its ramifications.

The Patient's Extrafamilial Interpersonal Relationship.—Ways of behaving at school, at work and at play throughout the patient's life plainly are of determinative importance to an understanding of the development and functioning of his personality.

Psychosexual Development.—Whether one likes it or not, the sexual drive motivates an astonishingly large area of human behavior. Therefore in any serious appraisal of a given personality the physician must consider as closely as possible the manner in which the attitude toward sex was formed and the particular coloring this attitude has given to sexual behavior. The psychosexual set is, patently, a facet of the patient's general interpersonal relationships and possibly the most important one. It seems scarcely necessary to add that this is not the same as saying that the best approach to a patient's problems is a frontal attack upon his sexual functioning.

Pseudohereditary Influences.—Certainty as to the role of genetics in

human behavior is difficult to attain. Observation of the modification or complete disappearance of "hereditary characteristics" justifies scepticism toward the all-too-easy tendency to ascribe specific behavior to the inheritance of definite gene patterns. Until conclusively proved otherwise, it is safer to assume that a patient's reaction during stress has been influenced by the diseases and/or stress reactions of significant persons that he observed in earlier life. The total setting in which he was exposed to such pseudohereditary influences may be of crucial importance for an understanding of his present illness.

The Patient's Evaluation of Himself—Does he consider himself inferior, superior or inadequate—and why? Self-evaluative remarks will stand out more and more clearly as he warms to the subject of his "life and times." Much information on this point can be gleaned by the manner in which he describes his relations with and his evaluations of others.

Dreams—The interpretation of dreams is not an easy task. Yet clues as to general trends are often enough obtained from dreams to make it worthwhile to request routinely that the patient relate such dream material as he can recall. Now and then, the manifest content of the dream will indicate that the unconscious wishes of the patient are remarkably different from his conscious thoughts. Thus the dream may serve as a useful stimulus for further and probably more revealing associations.

Interpretation.—As the patient talks, various patterns of reacting that are characteristic for him gradually crystallize. In this way opportunity arises for the physician to point out probable reasons for specific reactions in specific situations—to interpret for the patient the motives underlying his behavior. Probably the most difficult aspect of therapy, interpretation should be adjusted as nicely as possible to the expressed or felt needs of the patient at the moment. It is worthy of emphasis that the needs of the patient—not the needs of the physician—should determine the timing, phrasing, degree of depth and sweep, positiveness and other elements of interpretative comment. Time and place influences, in causal sequence, upon emotional reactions and their somatic concomitants usually are detected with greatest ease and accepted most readily by the patient. Acceptance is more likely, if the interpretation is presented tentatively in question form, rather than as a dogmatic statement. For the ultimate test of the soundness of the interpretation must be the pragmatic one. Does the patient feel that it is true? Is it something he can use for better self-understanding and control?

Interpretation also includes general aspects of psychotherapy that are frequently of major importance in the early stages. These are (1) acceptance and suggestion conveyed by word and attitude that the patient is worthwhile per se, that he has all the rights and privileges

common to all human beings and that he can be helped by the co-operative efforts of himself and the therapist, (2) giving correct information wherever the patient appears to need it in order to relieve him of anxiety occasioned by lack of, or faulty, knowledge—obviously called for in psychosomatic disturbances, in outspoken masturbation anxiety, and in many instances of unsatisfactory marital sexual functioning, (3) advice and help concerning desired readjustments of the daily regimen of living, including directions for relaxation training,⁴ suggestions for improved social, cultural and recreational outlets and assistance with any other phase of environmental management that may arise (here the aid of a competent social worker can be of great benefit)

GENERAL ORIGIN OF PERSONALITY DISTURBANCES

In order to practice medicine adequately a physician need not be a specialist in pathology. He can get along satisfactorily with a working knowledge of the origin of the specific disease he is called upon to treat and of its effect upon the functioning of the body. Similarly, he can approach disorders of the personality—that is of the total organism—with reasonable prospects of success, if he is oriented concerning the genetic and dynamic aspects of these disorders.

During the early years of life the individual is engaged in learning "the rules of the game"—what is permissible and nonpermissible behavior as he tries to satisfy his urge to live and his basic need to feel secure. If an untoward environment fails to provide the needed food, to satisfy the urge to live, the child obviously can be expected to exhibit tension. Likewise, if his need to feel secure through acceptance and affection is thwarted, tension is to be expected. *Vis-à-vis* the external world, the child is relatively helpless and dependent upon the wisdom and good will of others—the parents—for the satisfaction of his needs. The parents may lack the necessary knowledge, ability or desire to perceive and meet the child's needs. Hence, the latter may experience partial or complete frustration of his basic drives.

Frustration may occur because his behavior in attempting direct satisfaction of a strong drive runs counter to the standards of the parents and is condemned as "bad." To avoid the insecurity resulting from loss of love, the child tries to abandon his "bad" behavior by denying the existence of the underlying drive. Thus he forces a drive out of consciousness, in order to conform to parental command.

Such repression does not eliminate the drive from his personality, it remains in full force, but out of sight, and continues to seek satisfaction. In this way a conflict between a drive and parental prohibition develops. Because parental standards become adopted by the child as his own, so thoroughly that he loses awareness of their origin, the conflict, in effect, occurs between two aspects of his own personality—

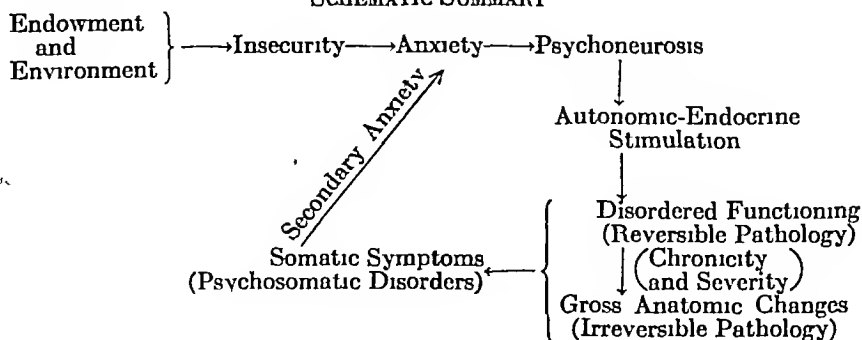
between his instinctual drives and what is now his "conscience." Such an "inner conflict" generates a feeling of inner tension which reaches consciousness as a sense of impending danger. This is known as anxiety, or apprehensive anticipation of some indescribable catastrophe.

Anxiety may be considered, then, as the underlying emotional reaction in personality disturbances. To be sure, anxiety may appear in several guises, yet the view that anxiety is the predominant reaction has value as a simplifying and unifying concept. It follows that the method used to control anxiety will determine the clinical features of personality disturbances. For example, when anxiety is controlled by being drained off—converted—into paralysis of an arm, conversion hysteria is seen, when control is exerted via a ritual performance—excessive hand washing—an obsessive compulsive neurosis is seen, when anxiety is not specifically fixed in an organized pattern, varied autonomic discharges accompany it, giving rise to psychosomatic syndromes.

The natural course of a personality disturbance may be summarized as follows:

Early environmental factors partially or completely frustrate the child's basic drives. A conflict develops within him which generates anxiety. He represses his drives in order to free himself of his sense of anxiety. Thus, the "gun is loaded"—the unconscious is burdened with a potent charge of anxiety. Later events that are emotionally traumatizing—for instance, death of parent, adolescent sexual experimentation, marriage, childbirth or loss of job—"pull the trigger," setting off an explosion of anxiety. Repression is no longer entirely successful, owing to the strength conferred upon the anxiety by the fact that the generating conflicts remain unconscious. Other methods of control must be resorted to and repeatedly renewed, as succeeding events that resemble in some way the traumatizing events stir up anxiety again and again. Once started, the process tends to be self-perpetuating until, ideally, the unconscious conflicts are restored to consciousness and finally resolved.

SCHEMATIC SUMMARY



CRITERIA FOR MAKING A DIAGNOSIS OF PSYCHONEUROSIS AND/OR A PSYCHOSOMATIC DISORDER

For practical purposes, it is useful to have simplified guideposts in mind as aids for organizing one's diagnostic thinking. With no intention of belittling the importance of the most thorough laboratory investigations where indicated, one can maintain that many such investigations are stimulated solely by failure to organize the data obtained from the patient in a meaningful way, and to ask what a particular test can be expected to reveal in the light of the whole picture.

Positive Criteria—These are fundamental, as a sound diagnosis must be based on more than exclusion.

1. Sense of insecurity in early life.
2. Anxiety experienced constantly or recurrently in certain or all situations and causing the patient to react excessively—i.e., to a degree that is not warranted by the objective facts.
3. Close time relationship between the anxiety-producing situation and the development of somatic symptoms.
4. Partial or complete subsidence of symptoms in anxiety-allaying situations.

Corroborative Criteria—Frequently the first interview or two will fail to provide sufficient facts to establish a diagnosis securely. Here, these criteria find their major usefulness.

1. Absence of structural pathology that could reasonably explain the symptomatology.
2. Presence of structural pathology—reversible or irreversible—that is generally agreed to result from chronic, psychogenically determined malfunctioning.

PSYCHOTHERAPEUTIC MANAGEMENT

Objectives—A rational approach to any therapeutic problem must be guided by awareness of what can legitimately be expected of the therapy. Therefore, the factors that may influence expectations should be appraised carefully during the initial interview, with the reservation always in mind that further acquaintance with the patient may force profound alteration of this appraisal. Some of the factors to be considered are:

Age—Roughly speaking, the age limits for best results with the conversational method are 16 and 50 years. For younger individuals, special techniques may be essential. With the middle-aged and elderly, emotional resilience is often so lacking that symptomatic relief is the utmost one can achieve.

Intelligence—At least average intelligence is requisite for significant gain from therapy, despite the fact that emotional conflicts

underly personality disturbances. The capacity of those with less than average intelligence to become mature personalities is obviously reduced, although a good emotional relationship with the therapist may enable them to carry on with much less suffering. Plainly, the better the intellectual capacity, the more likely that insight will be realistically applied and the more thoroughgoing the resolution of conflicts can be expected to be.

Education—Much the same comments apply to the educational status of the patient. The broader and deeper the educational background, the easier communication between therapist and patient will be.

Environmental Factors—Occasionally, factors in the patient's environment have a decidedly detrimental influence upon his emotional stability, so that gains from therapy are continually being nullified. If these factors are irremediable, therapeutic aims must be lowered.

With such factors in mind, the therapist tries to gauge whether he can hope to help his patient to more than symptomatic relief. Ideally, the objective is to help the patient to resolve his conflicts so completely that he will be able to live realistically in the present, and to cope, without excessive anxiety, with whatever stresses he may have to endure. Practically, the objective of giving as much symptomatic relief as possible is forced upon the therapist by circumstances beyond his control. To avoid frustration reactions himself, he should try to accept whatever objective seems dictated by each case.

Technic.—1. The general method of carrying on interviews has already been outlined. Its essence consists of permitting the patient to talk about himself, freely and without embarrassment. What induces him to reveal his "private world" to the therapist is the emotional relationship that develops inevitably in the therapeutic situation. This relationship, known as the "transference" relationship, supplies the drawing power of the therapist that enables him to help the patient bring out more and more completely the basic motivating forces of his personality. At the same time, the transference encourages the patient to look at himself more frankly than ever before, and hence to see himself more nearly as he actually is. Thus he gains an understanding of his problems that enables him to attempt changes in his behavior that had previously been impossible because he was unaware of what required changing.

When he finds himself occupying a predominant role in the patient's emotional life, the physician must recognize that it is not a cause of himself per se that this is so, but because of the special that is conferred upon him by the therapeutic situation. He constantly remind himself that he is, after all, only a sort of in which the patient sees, more or less sharply focused, all the ant drives of his whole life. If he is able and willing to accept

this role, the physician may gradually wield important influence toward emotional maturity

2. The mechanics of therapy have some bearing upon the development of a positive transference. If the patient is obviously in urgent need of help, it is wise to see him every day for an interview lasting from forty five to sixty minutes. As the pressure within diminishes, reduction in the frequency of interviews is often possible even to once weekly and, in the later stages, to twice or once per month. With many patients, satisfactory therapy can be carried on from the beginning with weekly interviews. Where circumstances dictate symptomatic relief as the only legitimate objective, interviews for the purpose of ventilation, explanation and reassurance may reasonably be spaced at intervals of three to four weeks.

Illustrative Case.—The following case abstract illustrates the positive and corroborative criteria for making a diagnosis, as well as the application of the technic of interviewing. It should be recognized that a short, clear-cut case was deliberately selected, and that not every case is as readily dealt with. Words in italics represent condensed interpretative comments.

This 30 year old, white, married male was referred for treatment because of severe diarrhea that had handicapped him for the previous six years. Numerous investigations had resulted in diagnoses of mucous colitis and ulcerative colitis. No regimen had ameliorated his symptoms, and he had become increasingly tense, jittery and despondent. While visiting friends five years previously, he had soiled himself and thereafter dreaded a recurrence of this humiliating experience. At times his fear had been so strong that he could not leave his home. A tendency to cry easily had troubled him for the past year or more. He was vaguely aware of a confused welter of thoughts and feelings that he was constantly fighting to keep out of consciousness. *He was told that his bowel reactions undoubtedly were associated with situations in which he felt increased tension and anxiety that increased peristalsis under such circumstances is common.*

He then pointed out that he had been inclined to suspect this from the onset of his illness, which he now believed had started early in his courtship over eleven years ago when he had visited his girl at the summer cottage of her parents. He had found her family quite distasteful and could scarcely be civil to them. He now wondered whether this was because of their working-class status which reminded him of his own working-class background, which he had been consciously trying since about age 10 to live down. This association stemmed from an episode in which he had been acutely embarrassed by his mother's behavior before a well-to-do schoolmate. The patient's mother had carelessly exhibited her habit of wiping her nose with the back of her hand. Noticing his friend's attention focused on his mother's action the patient rushed him out of the house only to have his friend ask him if his mother always did that. The patient felt humiliated and very resentful toward his mother.

Further associations revealed that the patient had long been troubled by his mother's uncouth habits, as well as by quarrels between his father and mother over finances and by their occasional overindulgence in liquor. He had been aware of feeling uneasy at home and had avoided bringing his friends home with him after school. He felt guilty because of his "bad" thoughts concerning his parents, yet vowed, after the humiliation referred to never again to let his friends see what

went on at home. Also, he decided that he would not live as his parents lived when he grew up, and that he would better himself financially and socially. *It was suggested to him that situations in which his bowel symptoms recurred might be those in which he felt that his origins were handicapping him or in which he felt defeated in his efforts to deny and escape them.*

This cue brought forth a profusion of incidents indicating his growing awareness of tension and anxiety in social situations. For example, He left high school in the spring of his senior year, because he could not tolerate the thought of permitting his mother to attend his graduation exercises, through well-to-do school-mates he gained admission to a select club after having described his father's occupation as "sculptor," instead of "stone-cutter."

A club member introduced him to the girl with whom the patient fell in love. He recognized that he was first attracted to her because his friend thought well of her. He set out to win her for himself, despite feeling guilty over his disloyalty to his friend. Having made some progress, he was pleased to be invited to visit her parents' cottage at the shore. When he arrived, saw the circumstances of their life and learned that her father was a laborer, he was nearly overwhelmed and at this time first noted loose stools. Although conscious of mixed feelings toward the girl, he persisted in his courtship, married, and strove to get ahead in business. After years of effort he felt that he was on the verge of being accepted socially by those he considered above him, when the soiling accident occurred after dinner at the home of one of his business superiors. *It was suggested that the accident occurred in response to his mixed feelings of guilt, because of his desire to renounce his parents, anxiety lest he fail to make the grade, and aggression toward his host for being more successful than he and, hence, for causing him so much striving and suffering.*

The patient later brought out fantasies concerning the relation between early masturbatory and adolescent heterosexual activities and his bowel difficulties and sense of inner confusion. He had speculated that his previous sexual practices had "ruined" his body and his mind, so that he had lost control of his body and was gradually losing his mind. *He was reminded that his bowel behaved quite well in situations that did not provoke anxiety, and that he had been reasonably successful in business, considering the emotional tension he had been laboring under.*

By this time, the patient had been seen five times over a period of six weeks. He had already stated that he was less depressed, that he was beginning to see the picture of himself taking shape, and that he could see a possibility of getting better. He now remarked that his bowel symptoms were practically nonexistent, that they were "kid's stuff," and that he had "bigger worries" to contend with—that is, resolving his conflicts concerning his parents and himself in relation to his supposed superiors. From this time on, the patient gained insight rapidly. Under the stimulus of the transference, he found it possible to accept himself as he was and to deal realistically with his present problems of looking after his family and getting ahead in his business. He was seen ten times during the first four months, once monthly for five visits, and then once in two months until he discharged himself fifteen months after his first visit. He has remained well for more than a year.

Results.—To label "cured" a person suffering from a psychoneurotic illness is hazardous, unless that person has shown, over a period of 12 months, ability to handle his life in a realistic, mature fashion without significant symptoms. However, the classifications "much improved," "improved," "moderately improved" and "unchanged" may be used to judge results. In an outpatient clinic to which all types of psychoneurotic and psychosomatic cases are referred, it has been possible

to average with all patients seen at least four times approximately 50 per cent "much improved" and "improved" results with many more falling into the "moderately improved" category. Of thirty-five cases of the "irritable bowel" syndrome, twenty-three could be classified as "much improved" and "improved," seven as "moderately improved," and five as "unchanged"—in other words, about 66 per cent were able to carry on their normal lives with no or few symptoms.⁵

Denker⁶ has collected figures on the results of treatment of the psychoneuroses which show that 60 to 70 per cent of patients are restored to completely or nearly completely symptom-free living after competent psychotherapy. He was able to show, in addition, from a study of a heterogeneous group of 500 neurotics who had filed disability claims and who had been treated solely by general practitioners, that 45 per cent were "apparently cured" after one year and that only 10 per cent were disabled after five years. While there may be legitimate criticism of the validity of comparing such cases with those who were seen without any question of a disability claim, these figures, nevertheless, suggest that the interested general physician can reasonably hope to help his neurotic patients.

SUMMARY

Psychoneurotic illness bulks too large in medical practice to be handled by specialists in psychotherapy. Much can be done to alleviate very real suffering by every physician who will familiarize himself with the general principles of personality development and functioning, and with a technic for helping a person to understand himself more clearly.

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TREATMENT IN CHILD PSYCHIATRY

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IN this brief presentation we aim primarily to outline important methods of treatment in child psychiatry with full awareness of the many different points of view prevailing in this rapidly growing and changing specialty. The augmented interest of the medical profession in child psychiatry stems from a growing realization that adult maladjustments are founded on emotional disorders of childhood. If nervous and mental diseases have a true beginning in the experiences of early life, more may be expected from a given therapeutic effort applied in the initial stages of disease than after nonadaptive behavior has hardened or crystallized. This has enormous implications for preventive medicine.

Classification of Childhood Disorders.—No satisfactory etiological classification is, as yet, available. The classification of diseases adopted by the American Psychiatric Association is designed primarily for adult disorders. There are differences between the neuropsychiatric disorders of children and adults. For example, there are no confirmed reports of sustained mood displacements in the years prior to adolescence analogous to the affective disorders of adults. Schizophrenia, so common in the adult population, is relatively rare in childhood, although not a few cases have been reported even in very early years. Kanner¹ classifies in the schizophrenic group "early infantile autism," a rare and very interesting disorder characterized by complete lack of interest in social and interpersonal relationships from birth. Numerous cases of brain damage with psychosis are found in childhood, resulting from such conditions as encephalitis, degenerative disease, brain injury and epilepsy. They frequently require institutional care and special therapeutic technics. Space does not permit adequate consideration of all these types of mental diseases in children. A classification of disorders commonly encountered in a busy clinic and not usually requiring institutional management is as follows:

- 1 Anxiety States (acute and chronic)
- 2 Compulsive States (acute and chronic)
- 3 Psychosomatic Disturbances
 - (a) Visceral (gastrointestinal or urinary tract)
 - (b) Motor (tics, hyperactivity)

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4. Social Disturbances.

(a) Withdrawal.

(b) Aggressive behavior, sexual perversions and other delinquent trends.

Treatment—The approaches to the treatment of children's disorders consist of (1) efforts to modify the child's environment (indirect therapy) and (2) direct psychotherapeutic work with the child. The two methods complement each other and should not be considered as mutually exclusive.

INDIRECT THERAPY

The indirect approach was originally the principal tool for dealing with children's problems. It is more productive of results than similar maneuvers with adults. The child is still in the formative period and habits of reaction are not rigidly established. Often with the removal of intolerable pressures, the child's capacity for growth asserts itself and unwholesome patterns are abandoned. On the other hand, alteration of abnormal attitudes in the child without environmental modification may yield transient benefits only. An adequate plan of treatment, therefore, usually involves some degree of environmental manipulation.

One of the ever present needs of the disturbed child is a modification of attitudes and unwholesome reaction patterns in individuals with whom he is in closest contact. Techniques for achieving this end have been improved greatly in recent years. Formerly attempts were limited to re-education of parents, but often it is not ignorance, of principles of child management which misleads parents but rather their own personality difficulties which interfere with the application of these principles. We have learned that for the effective management of parental difficulties it is necessary to employ as much, if not more, skill and caution in the interview situation as in any ordinary psychotherapeutic relationship. The tendency to ignore the principles of interviewing when we are dealing with parents is great because they do not complain of their own symptoms, nor ask for help for themselves. A common pitfall for tyros is to limit the possibilities of the relationship with the parent by immediately adopting the role of an authority and fountain of knowledge. Once this role is adopted, retrenchment is very difficult.

On the other hand, we may postpone the adoption of a specific role until the complexities of the situation unfold. The interviews with the parent may be opened with a general statement about the intricacy of the problem and the need for detailed information concerning the stresses in the child's environment and his reactions. The information obtained and the emerging attitudes of the parent thereafter determine our relationship with the parent. Often a careful review of the situation alone is sufficient to relieve anxieties in the parent and he begins to see

relations between the child's symptoms and his own behavior to which he was previously blind. If the parent fails to perceive the relationship between his behavior and the child's pattern of response, it may be necessary to point this out—as the interviews proceed.

In some instances the initial psychiatric interview will reveal deep-seated neurotic or psychotic trends in the parent which cannot yield to the simpler and more superficial therapeutic attempts. In such cases the parent becomes the main focus of attention and all the therapeutic tools utilized in adult diseases at once become applicable. Alleviation of such symptoms is imperative before the parent-child relationship can be worked through effectively.

The problem of who shall handle the parent and who the child in a clinic set-up is still a big issue. Many clinics follow the practice of having children seen only by psychiatrists and parents only by social workers, and if the parent is too disturbed, he is referred to a different clinic for psychiatric help. Others have found a more flexible approach advantageous, the psychiatrist treats the more disturbed member of the family and the social worker the less disturbed member. If then the parent falls to the psychiatrist, the latter plays a strong supervisory role in guidance of the child-social worker relationship. A common practice in some clinics is the limitation, if not avoidance, of contact between the child therapist and the parents of the child, a practice which has grown out of a realization that the child's relationship with the therapist is threatened when the child is aware that the therapist consults his parents. However, Rogerson² and Despert³ have each reported that the child's reaction to this threat can be utilized to advantage in therapy. In child analysis as described by Anna Freud,⁴ contacts between parents and analyst are frequent and intensive. The handling of both parent and child is often unavoidable in private practice. Although often successful, this technic invites more complications than the divided approach for it is not easy to avoid favoring one of the individuals either from the standpoint of interest or time.

Work with the child's parents or guardians is one of the most important elements in attempts to modify the child's environment, however, there are other measures which can spell the difference between success and failure in work with problem children. A rather drastic step, which nevertheless may be attended with most satisfactory results when rightly managed, is removal of the child from the home. This may be indicated in the following circumstances: (1) a parent openly rejects the child who is aware of this rejection and is disturbed by it. In cases in which rejection is more subtle and consciously perceived by the child (who in fact may thereby become more dependent on his parent) removal from the home may meet with failure because the child runs back to his parents. (2) A delinquent child lives in an unwholesome family group which greatly contributes

to such delinquency and is essentially incapable of modification (3) The mother is removed from the home by separation, divorce, ill health or bereavement, and an adequate mother substitute is not available

These indications may not be regarded as pat formulas to be utilized without thorough study of each individual case, for the removal of the child from the home is a momentous event both in the life of the child and in the experience of the responsible adults. Community facilities for dealing with such problems are being improved constantly as our understanding of children's needs increases. In general, where prolonged placement seems indicated, a foster home which is attuned to the needs of the particular child is the treatment of choice. Where the severity of the child's symptoms makes foster-home placement unfeasible, as in cases of serious delinquency, institutional care may be indicated. This measure has been used only as a last resort when all other measures have failed. In planning for institutional care we attempt, in so far as possible, to select those institutions in which an individualized approach to the patient under careful psychiatric guidance is used and where adequate planning for the return to the community is regarded as part of the treatment.

Where home situations are less critical, less radical prolonged placement plans are made to advantage. Boarding school placements in conjunction with summer camp are often helpful for the older child. Such plans are frequently preferred to foster-home placement because they are more socially acceptable. It is well recognized that the older child does not adjust as well as the young child in a foster home since his patterns of reaction to family life are less flexible and his affectional ties to substitute parents are likely to be weaker.

In many instances the problems of the child's maladjustment may best be managed by maintaining the home environment, and therefore the child's emotional constellation, relatively intact and making only minor modifications or adjustments in the total picture. Nursery schools, for example, answer the problem of the cramped crowded home, lack of play facilities and lack of companionship. For somewhat older children, clubs and recreational organizations encourage expression, channelize aggressive and competitive drives and teach identification with the group. It is important to make the initial contacts with the group easy, especially for the backward child, and to interpret the needs of the child to the club leader. Summer camps for children who are normally at home the rest of the year provide a welcome relief from minor chronic irritations and a wholesome atmosphere for further development. Consultation with the school authorities and interpretation of the child's problems often yield dramatic results, especially when frustrations and dissatisfactions stem from the school scene. We cannot expect the school organization to gear itself to the

child's needs, but a cooperative and resourceful teacher may invent innumerable socially acceptable ways for the child to obtain the attention and recognition he fondly desires

Special difficulties in children, such as reading disabilities and speech disorders, which may handicap a child in a very serious way and intensify existing neurotic trends are given special attention either within the clinic set-up or in the community. Unfortunately, community facilities for dealing with these disabilities are, as yet, very limited

DIRECT THERAPY

We have reviewed some of the important measures involved in molding the environment to suit the needs of the child. This approach, if used alone, however, even with the utmost caution and skill, has definite limitations. Attempts to modify parental attitudes or to manipulate the environment in any way are often frustrated because of the basic inability of the parent to cooperate in the total plans. There are many children in whom unwholesome reaction patterns have become ingrained and who continue to show symptoms despite more ideal external circumstances.

For such children some form of direct therapy is definitely indicated. Even with less handicapped children who show promise of a favorable response to an improvement in the environment, direct therapy is often useful. They can often profit from an opportunity to learn the role which their own conflicts have played in creating past difficulties and thereby become better equipped to handle frustrations and traumatic events in the future.

Until recent years our opportunities for dealing directly with children have been limited because of the fact that the child is so often inaccessible in the interview situation. The younger the child, the less the likelihood of his verbalizing his conflicts and difficulties. It is partly because of this fact that the environmental approach has in the past been developed and exploited to the extreme. Fortunately, pioneers in the field of child psychiatry have paved the way in recent decades for a more direct approach by utilization of play technics.

The methods of application of the play technic in therapy with children vary from clinic to clinic and individual to individual, however, certain generalizations are possible. With older children a few simple materials such as finger paints or games like checkers serve to reduce the threat of the interview situation and facilitate the establishment of a relationship. With the more blocked older children the same creations can serve as the starting point for discussion. Sometimes beyond the age of ten or eleven years might regard such an approach as too childish, artificial and indirect, an attitude which clearly minimizes the value of the technic. With the younger child

the possibility of establishing a relationship on the basis of the interview situations alone is often precluded. It is not only that the child expresses himself more easily and fully in play and action than verbally, but he is accustomed to testing reality and relationships in terms of activity rather than in words.

The usual treatment consists of a number of sessions with the therapist in which the child is permitted to express himself through play. It is generally agreed that, with the child whose symptoms are of considerable duration, the use of *free play* is indicated. The child is informed that he has free access to the materials in the play room and that he can do whatever he likes in that room, except for breaking lights and windows or injuring the therapist. It is advantageous to set the limits initially and to adhere to them as far as possible throughout the duration of the treatment. Further introductory comments depend on the child's age, understanding and problem. It is often helpful to state that other children find it easy to discuss their feelings of anger, fear or discomfort as they play and to reassure the child that he will be permitted to return at regular intervals to the playroom with the therapist.

The degree and type of activity on the part of the therapist after the introduction to the play situation varies with the philosophy of the therapist. In the classical analysis of the child, considerable stress is laid on interpretations. An attempt is made to work through with the child the deep-seated unconscious meanings of his play and behavior. When this technic is used the child must be seen daily for many months and anxiety which may be activated by one interview is handled in the next. Anna Freud,⁴ one of the pioneers in child analysis, has written extensively on child therapy and, although she utilizes considerable interpretation of unconscious material, her approach is slow and cautious, and environmental modification as an important adjunct to the analysis is emphasized. Other analysts, such as Melanie Klein, recommend immediate deep interpretation of the child's play. Deep analysis of the child can be utilized only by those who are expertly trained and is applicable to a small group of children because of the time and expense involved. In general, it is recommended only for extremely neurotic children who are resistant to other approaches.

In contrast to the above, Rogerson² and Gitelson⁶ have each reported independently on a series of cases which were treated successfully with a free play technic with minimal interpretation after other child guidance measures had failed. Their results are encouraging and certainly indicate that this approach, too, may have considerable value. Allen⁷ and his group put the emphasis not so much on interpretation of play in terms of past experiences but rather on the interpretation of the relationship between child and therapist. The problem child will attempt to use unwholesome patterns which are

characteristic of his reactions in everyday relationships. He may order the therapist around, may avoid participation in cleaning up, and may refuse to accept limitations such as that no toys can be taken from the playroom. The child is not reprimanded for this behavior, but the behavior is pointed out to him and an attempt is made to understand it. When he is assured of the therapist's acceptance and fondness for him and the fact that his untoward behavior will not be held against him, these trends diminish.

Modifications of the play technic in the direction of greater control of the situation (Levy) have been used with excellent results in cases of acute anxiety symptoms of recent origin, such as might arise from bereavement, accident, surgery or the arrival of a sibling, and in cases with monosymptomatic disorders such as car sickness and nightmares (Solomon,⁹ Conn¹⁰). The emotionally pertinent situation is reproduced in the playroom (by means of a family of dolls, for instance) and the child is encouraged to express his reactions.

This type of therapy has been criticized on the grounds that the child may reveal too much too early in the game. However, if the reaction of the child to the situation is watched carefully, if the play is kept to the third person and if the child is protected from too great enthusiasm on the part of the therapist, these approaches can be used to advantage. The more controlled method does not necessarily exclude the free play technic.

Another type of relatively controlled therapy utilizes the spontaneous art expression as the chief tool in treatment. This approach has been reviewed at length by Margaret Naumberg.¹¹ At the outset it may be necessary to utilize other approaches to gain the child's confidence. The chief emphasis in this treatment is the utilization of the child's creative art to uncover his conflicts.

In general it may be said that in the free play situation the degree of activity of the therapist is determined by the situation and the needs of the particular child. If a child is at first especially apathetic or inhibited, encouraging suggestions may be made about play or the therapist may begin to work with the clay hoping that the child will respond. There are many children who are more spontaneous, who seek out what they are interested in and ask for minimal participation by the therapist.

Where talk is limited, the therapist can encourage verbalization by letting the child talk about how the doll feels or tell a story about a model. We attempt to have the child keep the story in the third in the beginning in order to avoid creating too much anxiety. factors which seem to be of prime importance in effecting relief symptoms are the formation of a new type of relationship with adult who is permissive, tolerant and acceptive of the child, and the ability of the child to work out his difficulties in play without fear

of threats or punishment. Understanding of the meaning of the child's behavior is essential and it is of value to indicate to the child that he is understood. As the interviews progress and the relationship is strengthened, the child expresses his feelings more freely in work or play, and the therapist encourages such free expression, pointing out the universality of such feelings.

Play therapy with children is at times used as the only approach to treatment in situations in which other measures cannot be used. Children in foster homes who present serious neurotic symptoms which are not necessarily related to the present situation are most often treated by this method alone without much environmental manipulation or work with guardians. This is often indicated because it is extremely difficult to impose on the foster parent the obligation of bringing the child to the clinic and of being interviewed herself regularly. However, ordinarily, in children who live with their own parents, direct treatment is combined with interviews with the parents and with other environmental manipulation. In some cases the child is seen for only a few diagnostic interviews in the play situation and further work is limited to interviews with the mother. One advantage to the combined simultaneous approach is that the mother can be kept abreast of changes in the child and can be prepared for periods when symptoms may be exaggerated, as often happens in the course of treatment. Such a period, if not anticipated, might tend to discourage parents and result in their terminating treatment.

Termination of treatment with the child sometimes presents problems. As a rule, where progress has been made and the adaptation to his own world has improved, the child's interest in attendance at clinic diminishes despite a good relationship with the therapist. Often the move to terminate treatment comes first from the child. However, there are occasional cases in which the child does not seem ready to give up the relationship despite obvious success of the therapy. Often it is difficult to know what this attitude indicates but, in view of the community pressures at the present time, we should question the wisdom of prolonging the treatment unless it can be demonstrated that more is lost than could be gained by applying one's time and effort to more urgent problems.

GROUP PSYCHOTHERAPY

Group psychotherapy with children is a recent development which attempts to apply the lessons learned from individual therapy to several children at once. Benders¹² puppet shows portray emotional events familiar to every child such as sibling rivalry and parental punishment, and the children comment en masse at crucial points in the portrayal. Slavson¹³ recommends free play sessions for groups of children. The groups are small, usually four to eight children, and are

carefully selected in order to balance the aggressive with the withdrawn children. A therapist carefully trained to maintain a passive, tolerant, "neutral" attitude supervises the activities. It is claimed that this method yields gratifying results in cases with mild neurosis and behavior disorders in which the patient both lacks and desires socialization.

ILLUSTRATIVE CASE

The following condensed case report illustrates the problems and procedures in child psychiatry.

An eight old girl in the upper third grade was referred to the clinic because of spells of weeping and refusal to attend school. She had failed to attend school for a full month (excepting three days) prior to the clinic examination. At home she demanded a great deal of her mother's time and attention, wept whenever school was discussed, vomited whenever she anticipated leaving the house and slept restlessly. Both mother and child were the object of a great deal of criticism from all the relatives, many of whom felt that the child must be mentally unbalanced. The youngster would give no explanation for her behavior which kept the home in a constant turmoil.

In the initial contact both mother and child were extremely overwrought. The mother was tense, agitated, overtalkative, tearful, the child wept constantly and clung to her mother's side. It was immediately decided that the psychiatrist should handle the mother and the social worker the child. The decision was made on the basis that the mother was even more disturbed than the child and the fact that the child was fearful of exposing her problem before a doctor.

In response to her mother's prodding, the child at first tried to show off her academic attainments, the mother meanwhile lamenting a bad ending for her brilliant youngster. With some difficulty the youngster was finally persuaded to abandon the mother for a short time and join the social worker in play therapy. For a brief period, she showed marked inhibition, then over a period of sixteen interviews gradually began to relax, showed more interest in play and soon developed a very strong attachment for the social worker. Whenever her major problem was mentioned, however, the child blocked and changed the subject until the end of the series of play interviews when she spontaneously spoke of her intention of returning to school. During the whole period of therapy no particular interpretation was offered by the social worker for the child's behavior. At the point where the little girl expressed her desire to return to school, perceiving that this interest was accompanied by considerable anxiety, the social worker merely reassured the patient that she could return to school at any time she so desired.

Interviews with Mother.—In the beginning the mother's agitation was marked and there was constant reiteration of the presenting problem and how deeply disturbed everyone was about refusal of such a brilliant child to attend school. Reports on the child's psychological test, however, revealed only average intelligence. The mother was confronted with this fact after the third interview and her attitudes soon changed. She began to discuss her own ambitions for the child and to see the relationship between these aims and her own deprived childhood. She had been orphaned in infancy and was a state ward until she was 4 years of age when she was adopted. Her adoptive parents were kind to her, but she always felt inferior and under necessity to be unusually good to earn their love. She was insecure, anxious and fearful in her own childhood. From the beginning she felt that her sister Joan was like her and gave Joan much of the protection that she wanted for herself in childhood. She never encouraged socialization and had handled Joan

like a delicate flower Joan played little with other children. The mother always accompanied her child back and forth to school. The child was encouraged to apply herself to school work on evenings and week ends and her mother was always very disturbed at any inferior performance in her school work. The mother spent much time helping her child with her work, playing with her after school and devoting all her evenings to the child's demands.

It was interesting that the relationship of the mother to her other child five years older than the patient was completely different from that with the patient. The mother had experienced a psychotic depression after the birth of her first infant and that child was raised for almost a year by the maternal grandmother. After recovery from her depression the mother found her infant robust, happy and animated and she never, therefore, felt any anxiety about her. During the five years between the first and second child, the mother felt less secure in social relationships, partly because of her psychosis and also because of her financial status. Her husband's income was meager and most of her old friends had advanced considerably. She was preoccupied with making ends meet and economized at the expense of recreational outlets. She was happy throughout her second pregnancy but was psychologically set to satisfy her own ambitions through mobilization of the child's abilities.

The mother needed little help in seeing the relationship between her own attitudes and the child's behavior. Early in the course of contact she attempted to wean the child away from her and encouraged socialization. The child began to play with other children with zest and enthusiasm, obviously finding much satisfaction in these new activities. The mother ceased urging the child to attend school and reassured her again and again that it did not matter whether she did well in school or not. She also began to accept the fact that the child would do better in the lower third grade.

Toward the end of the period of contact the mother stated that the whole experience had been very worthwhile and that she felt as if Joan's resistance to school had been a blessing in disguise. She realized she would never have faced her own problem without a crisis of this sort. The mother began to go out with her husband and to build up social interests of her own. She was relieved of the terrible fear that Joan's behavior was an indication of serious mental illness of a hereditary nature.

When Joan indicated that she was ready to return to school, a visit was made to the teacher to interpret the child's difficulty. The teacher was most cooperative and showed considerable understanding of the situation. No issue was made of the child's absence from school, and she rapidly caught up in class activities.

Comment—This case has been selected for the following reasons

1. It represents an acute disturbance in parent-child relationship which has no particularly deep-seated psychosexual roots. These problems are not unusual in ordinary clinical practice and are highly susceptible to management by relatively simple techniques.

2. The case was dealt with almost entirely on the level of the present illness. The alpha and omega of therapy was the present acute disturbance.

3. "Teamwork" cooperation of patient, parent, social worker and school under the guidance of the psychiatrist is clearly illustrated.

The kernel of the child's problems was evidently an acute anxiety reaction, poorly verbalized, involving fear of failure in school work. The situation developed in a setting of overmobilization of the child's

energies under the condition of diminishing returns for energy expended, the latter an inevitable outcome of increasingly difficult school work. The manifestations of the child's neurosis were spells of weeping, stubborn refusal to attend school, frequent unexplainable morning vomiting, and disturbed sleep.

The mother's conflict centered about an inadequacy feeling resulting from unfortunate childhood experiences and insecurities concerning love of adoptive parents. She attempted to achieve compensations by proxy, an example of misapplied love for her child.

The psychiatrist treated the most disturbed member, namely the mother. Play therapy became the method of choice simply because in interviews the child was inaccessible due to overwhelming anxiety and her misconception that treatment was punishment. Play therapy further permitted free motor activity as a substitute for verbalization.

The dramatic consequences of this relatively simple type of management, both for the patient and the parent, point up the extreme relief of anxiety possible in acute parent-child disorders. Both parties achieved profound release of tension and thorough-going changes of attitude—the child through play therapy, the mother through verbalization—each with a stable, accepting, uncritical and sympathetic adult.

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PRESCRIPTION OF PHYSICAL MEDICINE IN OFFICE PRACTICE

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PHYSICAL medicine offers the internist or general practitioner many opportunities to render his patients effective symptomatic relief and often definitive therapy. Frequently this treatment can be successfully carried out on ambulatory patients who receive regular physical therapy in the office by qualified physical therapy technicians under medical supervision. In order to achieve success, however, it is necessary to prescribe physical therapeutic agents with as much accurate detail as is required of any other medical prescription. A background of knowledge of the physiological effects of physical agents is therefore necessary for correct selection of the various available agents. Another essential element of a proper physical medicine prescription is an indication for the technician of the nature of the disorder under treatment and the changes which can reasonably be expected to result from the prescribed therapy. The minute details of technical procedures can then be safely delegated to the technician with regular medical check-up as to progress. As a background for prescription writing we will consider some of the verified effects of physical agents on the various tissues of the body starting first with the skin.

PHYSICAL MEDICINE AND THE SKIN

Thermal Effects.—Physical agents are frequently employed to raise the skin temperature. One of the most common methods is that of conductive heating. By this method there is an exchange of molecular energy from the hotter object to the cooler skin surface, with a gradual temperature rise of the latter. As this is a comparatively slow method of heating, no important temperature changes subcutaneously can be effected with conductive heating unless there is a proper allowance for time and, as a general rule, thirty minute applications are the minimum requirement for adequate heating of the deeper tissues as well as the skin. The common examples of conducted heating are the use of the hot water bottle, electric pad and warm water soaks at a temperature not exceeding 113° F.

A somewhat more rapid and efficient method of increasing temperature depends on the absorption of radiant energy. When the skin alone is the structure to be heated, radiant energy should be selected of

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those wavelengths known to be absorbed completely by the skin. For this purpose infrared generators which emit primarily in the far infrared range with a wavelength greater than 1500 millimicrons are satisfactory. These invisible rays are absorbed by the surface of the skin and heating at a depth is effected only by the slow process of conduction previously mentioned. One usually, however, wishes to have a more penetrating type of heat, and for this purpose a luminous source of infrared energy is more desirable. The ordinary incandescent bulb of sufficient wattage is rich in the near-infrared rays which are transmitted through the outermost layers of the skin, thus having more efficient penetration and depth heating effect. Studies have shown, however, that even with the most penetrating wavelengths of radiant energy it is necessary to expose the part for thirty minutes or longer in order to achieve proper deep heating. Other technical precautions include proper choice of reflector so that the heating is even and the avoidance of heat loss by unnecessary drafts.

The most efficient means of heating the skin and at the same time the deeper tissues is by the conversion of high-frequency electrical currents into heat. These currents are known medically as short-wave diathermy, but are of similar wave bands as those employed in radio broadcasts. Although these high-frequency electrical currents can penetrate tissues, in the presence of normal circulation which allows for dissipation of energy, the temperature rise at a depth is similar to that of the skin so that we can rely on skin sensation of temperature to adjust dosage. The extreme high-frequency currents producing microwaves represent another method of heating by conversion of electrical energy to heat. Although penetration of living tissues varies according to wavelength of the energy involved, as far as our present knowledge is concerned, the only effects achieved are those relative to changes in temperature.

In prescribing physical agents for their thermal effect the physician in selecting the proper agents should keep in mind the necessity of normal skin temperature sensation to safeguard against burns, particularly when using high-frequency electrical currents. Other factors are concerned chiefly with the ease or efficiency of heating either large or small areas of tissues. It is usually more satisfactory to order treatment which can be repeated under your direction at home by the patient and for this reason there is much advantage in prescribing the simpler methods of heating.

Sedative Effects.—Relief of pain is one of the commonest indications for the use of physical agents. These agents may be applied to the skin and through counterirritant effects relieve pain of deep-seated origin. The mechanism of this action has been suggested by recent experiments showing that equalization of temperature gradient changes the pain threshold.¹ Cold has a sedative action and likewise

contrast therapy with alternating hot and cold applications. Successful counterirritant effects can also be achieved by histamine iontophoresis or more definite sedative effects from novocaine iontophoresis. Occasionally the erythema following ultraviolet irradiations is helpful in relieving pain and pruritus of certain skin conditions such as herpes zoster.

Bactericidal Effects.—Ultraviolet irradiation, particularly in the shorter wavelengths, has some definite power in killing bacteria in the air but is of very limited benefit in sterilization of the skin. Ultraviolet irradiation when combined with more penetrating visible and near-infrared energy is often of value in stimulating healing of sluggish ulcers. It is doubtful, however, whether this action is directly bactericidal. The benefit of general ultraviolet irradiation or heliotherapy in increasing body resistance to infection is still controversial.

EFFECT OF PHYSICAL AGENTS ON CIRCULATION

It is generally conceded that the beneficial effects achieved by physical agents such as heat, massage, exercise and electrical stimulation are achieved through the mechanism of circulatory reflexes. It is well known that the normal response to an increase in temperature of the skin and subcutaneous tissues is an increase in circulation. Hyperemia is obtained by an increase in the capillary bed, a faster arterial blood flow and at the same time improvement in venous and lymphatic return. Superficial capillary dilatation can also be achieved by massage and iontophoresis. The venous and lymphatic flow is increased by the deeper types of massage and particularly active muscle contraction. It should be remembered when applying heat that its effects are beneficial only in so far as the circulation is increased more by the heat than the increase of metabolism also associated with rise in temperature. Prolonged and intensive heating may have deleterious effects by increasing the metabolic needs beyond the ability of the circulation to adjust reflexly. Caution is especially necessary when high frequency electrical currents are used as it is possible to apply large amounts of electrical energy for conversion into heat.

EFFECTS OF PHYSICAL AGENTS ON MUSCLES AND JOINTS

Sedative Effects.—Presence of painful and excessive muscle spasm is one of the important indications for the use of physical therapy, particularly thermal agents. Prescription in these cases is necessarily rather empirical because of our lack of knowledge of the essential mechanisms of muscle spasm. Painful spasm accompanying traumatic or infectious inflammatory reactions may be incited by accompanying sensory stimuli arising locally. Changes in the thermal gradient may affect the pain threshold and thus relieve spasm, or the

of relief may be associated with more complex chemical and physiological reactions occurring with increase in temperature and circulatory changes. Slow rhythmical massage also is effective in relieving many types of muscle spasm, in other cases deeper stroking and friction motions may be necessary together with gentle slow, passive stretching or traction.

Spasticity of muscles secondary to central nervous system disorders such as Parkinson's disease or pyramidal tract lesions may be temporarily diminished by special technics of scientific relaxation together with controlled rhythmical active movements. Psychological factors are important in these cases and various forms of occupational therapy are useful to instill confidence as well as for improvement in kinetics.²

Strengthening.—Weak muscles with normal innervation are best strengthened by active exercises. Resistance should be graded to produce some fatigue which then results in hypertrophy and increased strength. The most rapid results can be obtained with heavy resistance, low repetition exercises,³ whereas endurance and slower increase of strength is achieved by use of low resistance exercises repeated a great many times.

Maintenance of contractile strength of denervated muscles can be best achieved by appropriate electrical stimulation. As electrical excitability is altered following denervation, currents must be selected which are adequate to produce maximum contraction of muscle. Although this treatment will not prevent atrophy of denervation, the degree of weight loss can be diminished and the return of power following reinnervation hastened.

Joint Mobilization.—Physical therapy properly prescribed is an essential part of the therapeutic program for patients with chronic arthritis and for patients recovering from extremity injuries. Joint function can be maintained physiologically only when motion is provided. Physical agents already mentioned may be used to diminish pain and muscle spasm and then motion is best given actively under supervision of a skilled physical therapist or the physician. The normal pattern of motion is often lost in the presence of pain and muscle spasm, so that muscle reeducation is necessary to develop coordination. As muscle strength is built up, increased joint range will follow provided an active inflammatory process is not progressing. A safe general rule is to use active exercises rather than passive in all cases if possible. Emphasis is always placed upon correct performance of exercises so that there is a minimum of irritation and a maximum of stretching and voluntary muscle contraction. Further details of prescription of physical therapy will be noted below.

EXAMPLES OF PRESCRIPTION WRITING

Rheumatoid Arthritis—As the present discussion is confined to those patients who are ambulatory, we need consider only the early and milder cases of rheumatoid arthritis. In these instances physical therapy may serve a preventive role by maintenance of muscle power and consequently preservation of joint function. The general aim of treatment is to first of all teach the patient the essentials of proper body mechanics both at rest and during movement. Attempts are made to remedy any postural defects and to increase the muscle strength if asymmetrical weakness is present. When some limitation of joint motion exists, the patient is instructed in the proper way to stretch joints carefully by specific active exercises which are the backbone of the physical medicine prescription for these patients.

Where pain is a limiting factor, a full maintenance dose of salicylates will act synergistically with therapeutic exercise. Another useful pain-relieving measure is local application of heat or a full tub bath or shower. The practical details of the prescription can be noted from the following example of instructions given to patients with mild or early rheumatoid arthritis involving multiple joints.

EXERCISES FOR ARTHRITIC PATIENTS

General Instructions—The proper amount of exercise and rest is essential in the treatment of most patients with arthritis. Exercise, when properly performed, serves at least three purposes: (a) increases the range of motion in the affected joint, (b) strengthens the muscles moving the joint, and (c) prevents deformity.

Specific exercises for each patient will be taught and supervised by a physical therapist; the patient will then repeat exercises daily as instructed. Although details vary for each individual depending upon the severity of the illness, the following general rules should be applied to all exercises for maximum benefit:

1. After learning the motions to be performed, begin with only one or two repetitions of each exercise and repeat 2 to 4 times daily as ordered. Every few days, when possible, gradually increase the number of repetitions of each exercise to a maximum of ten repetitions.

2. Rest should follow each series of exercises. As improvement occurs, the rest periods will be shorter and exercise periods longer.

3. All exercise movements should be done *slowly* and *carefully*. Each active movement should be done through as great a range of motion as is possible.

4. An increase in pain or excessive fatigue which lasts for more than two hours following exercise indicates that the exercise has been too strenuous and less repetitions should be performed at the next exercise session.

5. Perform only exercises checked and do them in the manner demonstrated.

Shoulders

1. Supine position with elbows comfortably bent, abduct the arms to shoulder level. (Do not move scapula or clavicle.)

- 2 Now from position of abduction externally rotate as far as possible (Point hands to head of bed)
- 3 Then internally rotate as far as possible (point hands to foot of bed) and return to starting position
- 4 Place each palm or forearm on top of head
- 5 Then bring elbows together in front and back again to sides
- 6 With elbows straight at sides lift arms forward and up over head to extreme elevation
- 7 Use pulleys as instructed

Elbows

- 1 Fully and forcefully flex and extend
- 2 Repeat above exercise with hand alternately in pronation and supination.
- 3 Add resistance of weights to exercise 1 as instructed

Wrists

- 1 With elbow flexed and fingers relaxed, completely extend wrist.
- 2 Now fully flex wrist.
- 3 With elbows flexed fully supinate
- 4 Now fully pronate.
- 5 Do radial deviation (lateral movement towards thumb)

Fingers

- 1 Make a tight fist
- 2 Fully extend fingers and spread apart
- 3 With distal joints of fingers relaxed fully extend at proximal joints (metacarpal phalangeal)
- 4 Full radial deviation of thumb, then move each finger in same direction individually
- 5 Oppose thumb to each finger tip, opening hand as wide as possible between each movement.
- 6 Gentle assisted stretching of contractures as specified

Neck

- 1 Recumbent Flatten cervical spine, chin down and in
- 2 Rotate head to left and right.
- 3 Flex neck laterally, chin straight ahead
- 4 Head traction as instructed——minutes——pounds

Upper Back

- 1 Lying with small towel under mid-spine, extend back against bed with knees flexed
- 2 Breathe deeply with prolonged inspiration
- 3 Breathe deeply against sandbag on chest
- 4 Breathe deeply while stretching ribs with hands

Lower Back

- 1 Gluteal setting Forcefully tighten buttocks and pinch together
- 2 Contract lower abdominal wall bringing pelvis up slightly
- 3 Alternate straight leg raising with feet in dorsiflexion
- 4 With hands behind lift head and shoulders off bed
- 5 Face down, raise head and shoulders off bed with back muscles

Hips

1. Abduction in internal rotation
 - a. Recumbent With knees straight and toes pointing slightly together spread legs laterally-
 - b. Standing Raise one leg then the other as far laterally as possible
2. Internal rotation:
 - a. Rotate entire extremity inward (toes pointing together)
 - b. Standing, feet 12 inches apart, turn foot and leg inward and outward
3. Fully flex the hips and knees alternating each leg
4. Extension
 - a. Face lying lift thigh off bed
 - b. Standing with trunk stationary move thigh backwards.
5. Stationary bicycle riding

Knees

1. a. With pillow under knees lift heels till knees are straight without hip motion,
- b. Sitting on edge of bed, straighten leg
- c. Repeat with weights on feet as instructed.
2. Face lying, fully bend knee.
3. Back lying with hips flexed, flex and extend knees as though riding bicycle.
4. Stationary bicycle riding as instructed.

Ankles and Feet

1. Full dorsiflexion and slight inversion
2. Repeat with toes curled downward.
3. Circling motions of ankle through dorsiflexion, inversion, plantar flexion and eversion.

This outline of exercises is intended to serve simply as a working guide. It is valuable only when the patient receives proper individual instruction in performance of exercises. For joints with contractures more detailed instructions will have to be given as to the extent of exercises and their performance together with measurement of joint range so that proper progression of treatment or record of progress is possible.

Fibrositis—This term is used with some hesitation as it applies more to a clinical syndrome than to pathological classification. There are, however, many patients with disabling symptoms referable to subcutaneous and muscular tissues without evidence of true joint disease who are benefited by physical medicine. The characteristic complaints are those of pain, usually fairly sharply localized to a particular area of muscles, within which there are points of extreme tenderness on palpation. The commoner sites are in the muscles of the supraclavicular region and the paravertebral muscles, particularly those at the medial and inferior border of the scapulae. Patients with shoulder girdle localization are of particular interest because the pain often radiates downward over the arm and may be confused with bursitis, tendinitis, or lesions of the brachial plexus. The pain may also radiate

upward to the neck and even cause headache suggesting intracranial disease. When the lesion involves the posterior neck muscles acute torticollis frequently results.

The history of onset often reveals a preceding trauma which may either be a mild strain from heavy lifting or stretching or in other cases a direct blow to this area or fall upon the back of the neck with sudden twist or flexion. In other patients episodes of pain and spasm follow exposures to draft, and in still others there is an element of chronic postural strain from poor head and neck mechanics. Other common complaints include statements of inability to relax with feelings of chronic tension and fatigue. Stiffness of muscles or "jelling" following periods of inactivity are frequently reported.

Upon physical examination there may be observed some shortening of the muscles at the site of pain, particularly of the upper trapezius. Palpation reveals undue tenseness and sensitivity upon mild compression, deeper exploration reveals areas of increased resistance often nodular in character, and these round, firm, tender masses may be moved freely under the finger.

Physical Medicine Prescription—Massage when expertly given is the most valuable single procedure. When treatment is started soon after the onset of symptoms deep kneading, compression and manual stretching of the muscles under the fingers and circular friction motions very often result in relief of spasm and pain within a few minutes. The massage is usually painful at first but, unless the symptoms are too acute, should be persisted in and soon relaxation occurs. This can be perceived at once through the fingers of the operator. Heavy massage should then be immediately stopped and followed only by light sedative stroking.

At this point some local hyperemia exists with increase of skin temperature. This should be maintained by application of heat either through use of radiant energy or diathermy. With those cases where symptoms have persisted for several days or weeks it may be necessary to diminish sensitivity by first applying heat before the massage and then reapplying it after muscle relaxation has been obtained.

Any postural defects should be corrected by appropriate exercises. In some patients with chronic poor posture head traction with comfortably fitting sling holding the chin horizontal and the cervical spine straight should be applied with weights from 5 to 15 pounds, fifteen times, three times a day.

Occasional cases may be too acute to tolerate any massage and also some chronic cases with localized tender areas resistant to this treatment. Temporary relief of pain may be secured by means of novocaine iontophoresis. The solution used is as follows: procaine hydrochloride, 1 gm., epinephrine as bitartrate, 0.005, alcohol 80 per cent to make 100 cc. The pad is moistened with this solution over which a

small metal electrode is firmly bandaged and connected to the positive pole of the source of direct current. The negative pole is connected to a larger dispersive electrode. The milliamperage which can be used varies with the area of the smaller electrode and should always be within the comfortable tolerance of the patient. Figures may vary between 4 and 20 milliamperes with the average duration of application varying between 10 and 20 minutes. Local anesthesia need not be complete for relief of the muscle spasm and pain, but is usually sufficient to allow active exercises and full lengthening of the muscles previously habitually contracted. The frequency of treatment is an individual decision. An occasional case can be dramatically relieved with a single treatment, others may require multiple treatments over several weeks. Recurrences are not uncommon but may be prevented by teaching improvement of posture or in other cases specific muscle relaxation techniques.

Periarticular Lesions—There are still many other patients with symptoms referable to joints and surrounding muscles, particularly in the region of the shoulder, back and feet, who are benefited by physical medicine. One of the biggest problems is that of shoulder pain with limitation of motion due either to bursitis or tendinitis. Physical therapeutic methods of treatment for these patients are well known and need not be repeated in detail. One of the commonest prescriptions is for diathermy, either with short-wave technic or conventional long-wave diathermy. Many cases of acute bursitis, however, do not respond favorably to diathermy, which causes an increase of pain, perhaps due to overstimulation of the inflammatory reaction. Some patients get more symptomatic relief from application of cold or milder superficial heating with radiant energy. Various procedures may be tried for relief of pain, which is of utmost importance in order to prevent adhesions and restrictions of motion. Although rest is of importance in the early cases, exercise once a day when carefully done may prevent the onset of a chronic adhesive bursitis. In the latter instance the period of disability is usually of long duration.

Physical therapy may be successfully combined with other measures including irrigation with novocaine and saline to remove calcium deposits or operative surgical removal. An occasional case may require manipulation. In all instances a carefully supervised exercise program is essential for regaining free coordinated and strong shoulder movement. Physical therapy alone is usually not sufficient to control the pain of acute bursitis or tendinitis and the use of salicylates and other non habit-forming pain relieving drugs should not be omitted.

Backache.—The diagnosis and treatment of back pain is beyond the scope of this paper. The differential diagnosis between arthritis, ruptured disk, tumor and mechanical causes of back pain may require considerable study and elaborate procedures. A trial of so-called

conservative treatment consisting of rest and adequate physical therapy may aid in reaching the correct diagnosis or it may bring the patient relief of symptoms without benefit of a diagnosis. The measures used in these cases consist in bed rest with proper back support on a firm surface, adequate analgesic drugs, local use of heat for relief of pain, and occasionally sedative massage. As soon as muscle spasm is relieved gentle setting exercises for the low back, gluteal and abdominal muscles aid local circulation, prevent disuse atrophy and hasten mobilization. When the patients start walking it is of utmost importance to teach them proper back mechanics by means of instruction before a mirror and learning to contract individual muscle groups. In this way proper coordination may be developed together with increased muscle strength. Frequently careful examination reveals contractures of muscle groups, particularly the hamstrings and the tensor fascia lata. Gradual stretching of these structures may bring about permanent relief of recurrent backaches in patients whose pain is related to these mechanical defects. In other patients with definite rupture of intervertebral disk success from operative removal is made more certain by proper postoperative care including an exercise program beginning in recumbency and graded with convalescence until the back muscles are normally strong and properly coordinated with automatic normal mechanics.

Degenerative Arthritis.—A considerable group of patients has symptoms referable to degenerative joint disease. Although physical therapy cannot be thought of as curative, it probably is of as much benefit as any treatment available. Without describing the prescriptions for individual joints affected with degenerative arthritis it is perhaps sufficient to indicate the general principles which apply in ordering physical therapy for this group of patients. Pain is usually the symptom which brings the patient to the doctor for treatment, and certainly measures should be included to bring relief for this pain. They are, first of all, rest or diminished activity of the joint for short periods of time as compared with longer periods in the patients with rheumatoid arthritis. Application of heat locally of mild intensity also diminishes pain, but as these lesions occur more commonly in the older age group, dosage must be carefully regulated if there is any indication of diminished blood supply from arteriosclerosis, particularly in the lower extremities.

The only definitive measure is that of increasing support of the affected joints by strengthening the musculature through properly graded resistance exercises. Irritation of the joint such as by weight-bearing must be avoided during the exercises. In addition any aid to proper mechanics of the joint should be included such as lifts on heels to change the alignment of the knees, and instruction in postural correction. Another general principle of treatment of these

cases is to avoid unnecessary trauma associated with overweight or strenuous activities. These patients are rarely completely cured of symptoms and accordingly should be instructed in simple home procedures in physical therapy such as the use of heat, gentle sedative massage and, most important, continuing the necessary exercises for weakened muscles. Another measure which can be used profitably in the home is head traction for cases with degenerative arthritis of the cervical spine.

SUMMARY

1. Prescription of physical medicine should be specific, detailed and based on knowledge of physiological effects.
2. An adequate prescription should include (a) Diagnosis. (b) Agents to be used with details of application. (c) Effects to be produced. (d) Duration and frequency of treatment.
3. Some prescriptions for office treatment of arthritis and other musculoskeletal disorders have been discussed.

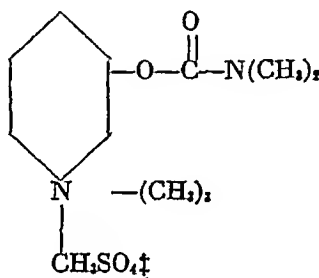
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(4) CLINICAL USES OF NEOSTIGMINE

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NEOSTIGMINE (U S P), also called prostigmin (Roche) in this country, is an effective stimulant of smooth muscle. In general, its effect is comparable to that of stimulating the parasympathetic nervous system. Neostigmine was first synthesized by Aeschlimann¹ in Basle, Switzerland, in 1931, in an effort to obtain a drug less toxic than physostigmine (eserine) but with the same effect on the intestine. This synthetic compound has the following formula:



The purpose of this communication is to assess the effectiveness of this drug in a variety of clinical conditions for which it has been used §

From the Medical and Neurological Services of the Massachusetts General Hospital, Boston, and the Harvard Medical School

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§ In place of the methylsulfate radical (underlined) which is the formula for the intramuscular preparation, the tablet for oral use has a *bromide* radical.

§ The following forms of neostigmine methylsulfate are available for parenteral injection: 1 cc. ampules in two strengths—1 2000 (0.5 mg per cc) and 1 4000 (0.25 mg per cc), a combination tablet with morphine containing 0.5 mg of neostigmine methylsulfate plus 8 mg ($\frac{1}{8}$ grain) morphine sulfate, and a special ampule for the diagnosis of myasthenia gravis (Neostigmine Diagnostic Ampule), containing 1.5 mg neostigmine methylsulfate plus 0.6 mg ($\frac{1}{100}$ grain) atropine.

Neostigmine bromide is available in the following forms: scored tablets for use, 15 mg per tablet, and a 5 per cent aqueous solution in 7.5 cc vials for thalamic use.

Neostigmine bromide given orally is one-fifteenth as effective as neostigmine methylsulfate given parenterally, i.e., one 15-mg tablet has about the same effect as an injection of 1 mg.

It is important to note that the amount of bromine in each tablet is less than 4 mg. of bromine. Even with doses as high as 300 mg of neostigmine bromide daily by mouth, the amount of bromine is only 75 mg. ($1\frac{1}{4}$ grains) per day. Such an amount of bromine has no sedative effect and is unable to produce bromidism in any of its forms. (On four patients taking this amount or more of neostigmine bromide, the serum bromide tests were negative.)

PHARMACOLOGY

Neostigmine and physostigmine act in the same way. Both depend on the presence of acetylcholine. According to Loewi,^{2a} Dale³ and Nachmansohn,⁴ there is strong evidence that, in the nervous system, transmission of the impulse from one neurone to the next depends on a formation of acetylcholine at the synapse. This chemical transmits the impulse to the next neurone, and, at the end of the chain, to the ganglion cell in smooth muscle or to the end plate in striated (voluntary) muscle. There is present at these points cholinesterase, which immediately destroys the acetylcholine and allows the synapse or motor end plate to rest until the next stimulus arrives. This process occurs throughout the entire central and peripheral nervous system except in the *postganglionic* sympathetic nerves which have their own chemical mediator, *sympathin*.

The pharmacological effect of neostigmine and its natural analogue, physostigmine or eserine, is that of depressing the amount of cholinesterase present in the serum. In other words, neostigmine, by depressing the esterase, strengthens the action of acetylcholine on the effector organs. This effect, in the post-ganglionic fibers going to smooth muscle, is similar to the action of a drug called muscarine and is called "the muscarine effect." The effect on the nerve endings in striated (voluntary) muscle is similar to the early action of nicotine and is called "the nicotinic effect of the neostigmine." The postganglionic nerves going to smooth muscle, and the motor nerves going to striated muscle, are called cholinergic nerves. It is important to note, however, that the nerve supply from the central nervous system to the sympathetic ganglia is also mediated by acetylcholine and are, therefore, cholinergic nerves.

Neostigmine increases glandular secretion including salivary, gastric and sweat. It stimulates smooth muscle, causing constriction of the pupil, increased motility of the stomach and intestinal tract, and contraction of the bladder. It also dilates most of the blood vessels, affecting arterioles rather than capillaries, particularly in the periphery, and in the large vascular beds throughout the body. The effect of neostigmine on all these smooth muscle systems is included in the muscarine effect of the drug. The nicotinic effect on voluntary muscles

is the basis of the effectiveness of this drug in myasthenia gravis.^{*} In this disease there is considerable evidence that the mechanism is an imbalance in the chemical processes of the motor end plate. Where there is no disturbance of end plate physiology, neostigmine has no beneficial effect on striated muscle whether healthy or diseased. On the other hand, Riker and Wiscoe⁴ have shown in cats that neostigmine, if the concentration of the drug is high, acts directly on striated muscle. It does this in the same manner as acetylcholine, causing the muscle to contract. They showed that even when all cholinesterase is removed by perfusing with di-isopropyl fluorophosphate this effect is still present. Furthermore, still larger doses of neostigmine produce a curare-like effect. They used doses of six to ten times that used in the clinical application of neostigmine and injected the drug into the artery.

For a more complete discussion of the pharmacology, the reader is referred to Goodman and Gilman's textbook.⁵

THE EFFECT OF NEOSTIGMINE ON THE NORMAL HUMAN SUBJECT

Neostigmine methylsulfate, 0.5 mg, injected intramuscularly usually has no effect on the healthy adult other than to produce a few degrees rise in skin temperature.²² This has been shown clearly by Perlow and is an important effect.

If 2 cc of the aqueous solution containing 1 mg of the drug is injected into the average human, a certain number of both subjective and objective signs can be noted. There is a small increase in the amount of sweating and the skin is slightly warmer. There is a slight increase in salivation and, in some subjects, this is evidenced by a slight thickening of the speech and a subjective report that the tongue feels full. Increased peristaltic movements in the intestines and in the stomach are observable by barium fluoroscopy or auscultation and, in about half the subjects, an awareness of this intestinal peristalsis is reported. A few of the subjects have a desire to urinate, belch or pass flatus. In about one-fifth of the subjects examined, small fibrillations are seen in the lateral aspect of the tongue. In about 10 per cent of normal subjects, small twitchings (fasciculations) can be seen in the arms or shoulders, if properly elicited. These can be demonstrated by the electromyogram. Voluntary power of a muscle measured ergographically is the same as before injection.⁶

If 1.5 mg is used, the effect in normal subjects is more severe. Salivation is more marked, there may be subjective blurring of vision, the smaller pupils, sweating and flushing of the skin is marked. More intense stimulation of the intestinal tract is shown by belching, increased peristalsis, and the desire to defecate or to pass flatus. Fibril-

^{*} Reference to much of the valuable physiological and biochemical experimental work is left out because of the limited scope of this paper.

lations are easily seen in the tongue and in the extremities. The patient may feel dizzy, complain of headache and pulsations in the vessels of his scalp. He may feel nauseated and have very disagreeable sensations in his limbs with a tremor. The general appearance of the patient is closely similar to that seen in seasickness—he appears ill with extreme pallor, the so-called “green” appearance. He may feel faint, lie down, and then complain of cramps and violent peristaltic motion. In some individuals, the fasciculations in the muscles and in

TABLE I

REACTIONS TO VARYING DOSES OF NEOSTIGMINE IN NORMAL AND ABNORMAL PERSONS

	Controls			Psychoneurotics or S S *	
	1 cc. (0.5 mg.)	2 cc. (1 mg.)	3 cc. (1.5 mg.)	2 cc.	3 cc.
Vertigo	0	0	0	+	++
Headache	0	0	0	+	++
Blurred vision	0	0	0	0	0
Tightness eyes	0	0	+	+	++
Salivation	0	+0	+	++	+++
Heavy tongue	0	0	+	+	++
Thick speech	0	0	+	0	++
Tremor of tongue (fibrillations)	0	+0	+	+	+
Tight throat	0	0	+	+	++
Abdominal cramps	0	0	0	++	++
Nausea	0	0	0	+	+
Subjective borborygmi	0	+0	+	0+	++
Desire to defecate and desire to urinate	0	0	+	+	++
Trembling limbs	0	0	0	0	+
Fasciculations of hands	0	0	0	0	+
Unsteadiness	0	0	0	0	0
Faintness	0	0	0	0	+
Weakness	0	0	0	0	+
	0	3	8	13	27

* S S = Subjects constitutionally susceptible to motion sickness.

the tongue will be pronounced and the patient may complain of them subjectively. The amount of work done by voluntary contraction of any of the muscles is less than before injection owing to the systemic disturbance just described. There is a diminution of muscular efficiency, if measured by quantitative means.⁷

Larger doses of neostigmine, injected into a normal subject, will increase the symptoms just described until toxic or dangerous levels are reached. A larger dose than 1.5 mg. is *never* used in diagnostic tests because of these risks. In fact, 1 mg. is the largest dose usually used

unless atropine is given to protect the subject against the intense stimulation of the smooth muscle systems in his body. If $\frac{1}{100}$ grain (0.6 mg) of atropine sulfate is used with 15 mg of neostigmine on a normal subject, the unpleasant muscle-stimulating effect usually will be avoided and the general complications and effects described in the previous paragraph are so reduced that they do not bother the average person. The reactions to various dosages of neostigmine are shown in Table 1.

The reaction of healthy individuals to neostigmine may vary from subject to subject. A small number of normal individuals show sensitivity to this type of parasympathetic stimulation and may have marked reactions.⁶ A preliminary study by one of us (R S S) showed that in a group of 100 subjects complaining of seasickness those susceptible to motion sickness by constitutional predisposition have a sensitivity to neostigmine. It was also noted by R S S that patients suffering from chronic psychoneurotic conditions of one sort or another tend to be more sensitive to neostigmine injection than normal controls.⁷ These studies need further confirmation.

EVALUATION OF THE EFFICACY OF A DRUG

The evaluation of a drug as a therapeutic agent is a difficult task. The patient with a chronic illness is too apt to exaggerate the benefits of treatment and his physician is apt to share in this enthusiasm. Consequently, in the medical literature, there is a great deal of inaccurate information concerning the benefits of therapeutic agents. This is especially true since more conservative physicians often do not bother to disprove overoptimistic claims or to submit their negative reports, which require compilation and effort, to the journals.

Standards.—We suggest the following standards for evaluating the efficiency of any drug.

1. There should be some specific or pharmacological reason for the use of the particular drug.

2. The effect of the drug should be clear and specific. It should not depend on another form of treatment in conjunction with the drug, nor should it occupy a subordinate position, if another drug is used.

3. The substitution, without the patient's knowledge, of a placebo drug in identical form should produce none of the favorable effects that are attributed to the drug.

The favorable effect of the drug in a particular disease should under all conditions be in the hands of different workers and

and not be subject to seasonal, regional or individual aptitudes. Schwab and Skogland have gone into this in detail with the claims Vitamin E⁶).

⁶ Six-tenths mg of atropine sulfate injected intramuscularly or even intravenously will promptly neutralize the excessive reactions of neostigmine.

CARDINAL DRUGS OF PRACTICE

With these four criteria in a single test, the effect of neostigmine in a variety of conditions will be revealed more fully. These conditions are discussed in the order of accepted therapeutic effectiveness and adherence to the four criteria outlined above.

Gastrointestinal Disorders.—The extensive action of neostigmine on the motor and secretory functions of the digestive tract and its value in treating certain gastrointestinal disorders are well established. Its mode of action, effective dosage, indications and contraindications in gastrointestinal conditions and agents compared to other similarly acting drugs will be discussed.

Mode of Action.—Neostigmine increases intestinal contractions, increases bowel tone and by stimulating peristaltic activity speeds up the forward movement of the gastrointestinal contents. In addition, it acts as a stimulant of the secretory cells of the stomach, pancreas and small intestine. It directly stimulates neostigmine accomplishes this by its inhibitory effect on the enzyme, cholinesterase.

Figures 154 and 155 show the excitatory action of neostigmine on the upper part of the small intestine as determined by the multiple balloon technique. The patient T. J., a 54 year old housewife was given neostigmine 1 mg. intramuscularly. Fig. 154. In ten minutes the intestinal contractions began to increase in frequency and amplitude in all areas studied. This increased activity, accompanied by transient nausea, continued for one hour, at which time an intravenous injection of atropine was followed by prompt diminution in contractions (not shown in tracing). Atropine apparently blocks the effect of acetylcholine by preventing its entering the effector cell. In the second patient, M. M., a 45 year old housewife, the effect of intramuscular injection of neostigmine (1 mg.) was more striking (see Fig. 155). Activity was largely sustained for fifteen minutes. Then suddenly large sustained contractions began, accompanied by sharp crampy upper abdominal pain. One minute later the patient felt nauseated. Five minutes after the onset of action, atropine 0.5 mg. was given intravenously, to relieve the severe discomfort. With the decrease in contractions similar to that from the atropine effect, pain disappeared but not before the patient had vomited. In general, an excitatory effect occurs in ten to thirty minutes after subcutaneous or intramuscular injection of neostigmine.

Neostigmine may be a more effective activator of peristalsis when given in combination with other excitatory drugs than when given alone. Adler and associates found that the expulsive action of the colon was greatest in response to the following combination: neostigmine methylate 16 mg. (0.25 mg.), ergotamine tartrate 0.5 mg. and pilocarpine 1.25 units. When each of these three drugs was administered alone, the neostigmine was found to have the most pronounced effect.

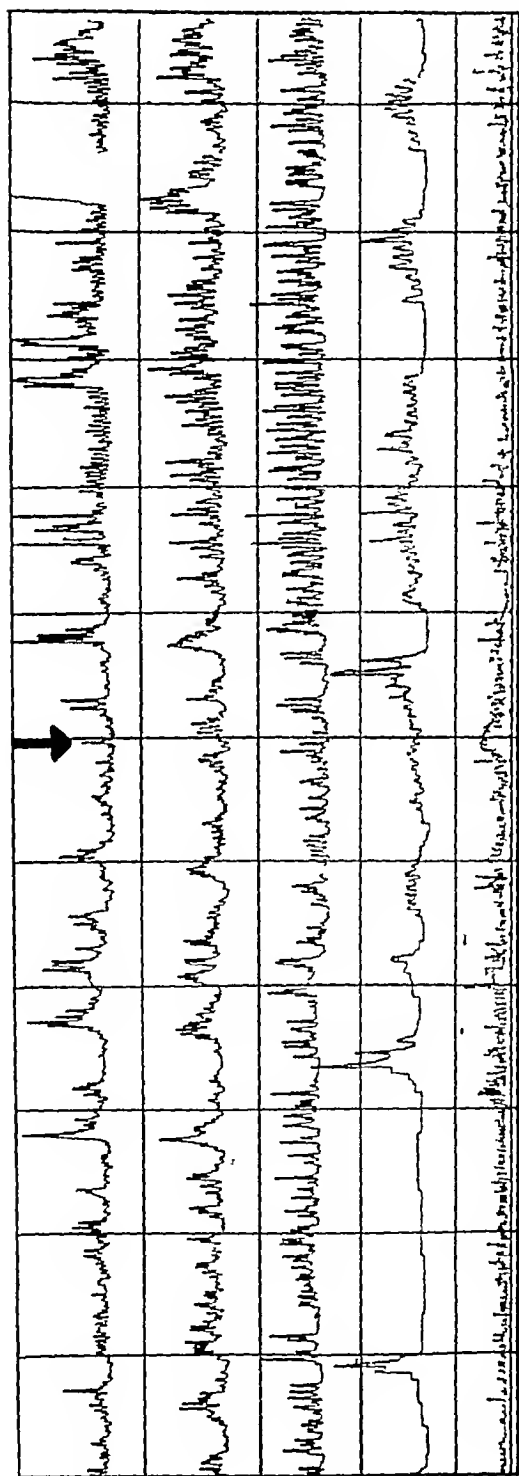


Fig 198 —A four balloon tracing of contractions in the upper part of the small intestine. The balloons were spaced at 5 inch intervals, each balloon being connected to a separate watermanometer and the pens writing directly beneath each other. Following a one-half hour control run, neostigmine, 1 mg., was given intramuscularly. Increased contractions were clearly evident ten minutes following injection. Chest movements are recorded at bottom of tracing. The vertical lines are spaced at five minute intervals.

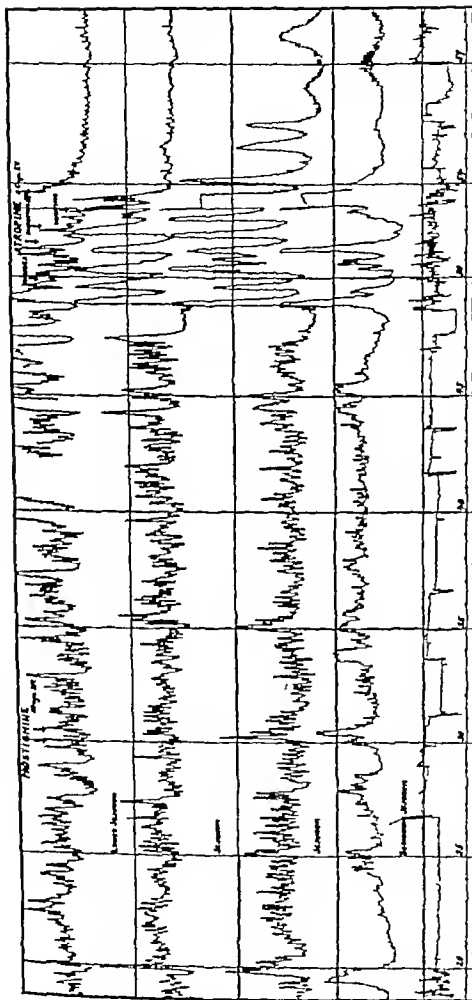


Fig 109—A multiple balloon tracing of jejunal contractions. Following a one-half hour control run, neostigmine, 1 mg was given intramuscularly. Eighteen minutes later marked increase in contractions occurred starting with the proximal balloon and progressing in a forward direction. Atropine, 0.6 mg intravenously, as shown in tracing, was followed by decrease in contractions in about two to three minutes. Respirations are recorded at the bottom of the tracing. The vertical lines are spaced at five minute intervals.

When used with atropine, the excitatory action of neostigmine is lessened. The combination of neostigmine (15 mg) and atropine (0.6 mg) subcutaneously rarely produces symptoms attributable to hyperactive contractions. According to Wolf,¹² this combination is a sufficiently potent excitant of gastric contractions to prevent nausea resulting from vestibular stimulation with ice water. When injected after morphine administration, neostigmine is said to counteract the paralyzing action of that drug.

The striking effect of neostigmine bromide (30 mg) on gastric secretion has been shown by Wolf and Wolff¹² in a subject with a gastric fistula. Within fifteen minutes after introduction of the medication into the stomach, the gastric mucosa became hyperemic, thirty minutes after medication, the acid output increased five-fold over its usual normal level and remained elevated for one and one-half hours. Pancreatic and intestinal secretions are likewise increased by neostigmine.

CLINICAL USES—Neostigmine is employed in many gastrointestinal disorders, its principal uses being as a prophylactic and, more frequently, as a therapeutic measure in combating postoperative distention. It may also be used in a variety of medical conditions in which abdominal distention is a prominent feature.

The reports of the use of neostigmine in preventing or lessening postoperative distention have been uniformly favorable. A general criticism of these publications is that adequate control data often have been lacking and little attempt has been made to quantitate the amount of distention present. An exception to this criticism is the report by Gordon^{9b} of 239 surgical patients, 98 of whom received neostigmine immediately at the conclusion of the operation, and 141 of whom did not receive neostigmine and therefore served as controls. The operative procedures consisted of appendectomies, removal of the gallbladder, laparotomy for gynecological conditions, and repair of hernia. The degrees of distention were placed in three categories as mild, moderate or extreme. The neostigmine-treated cases were then divided into two groups, those receiving the drug at four, six, eight hour, or longer intervals, and patients treated at two hour intervals. In each group, 1 cc of 1:4000 solution was administered subcutaneously. In the control group, in which the patients were treated by the usual measures for postoperative atony, distention occurred in 73 per cent. The patients receiving 1 cc. of neostigmine in four to eight hour intervals for six doses had an incidence of distention of 64 per cent, while those patients given six doses at two hour intervals showed only a 17 per cent incidence of distention. These data would indicate that the effectiveness of neostigmine is striking in those patients who were treated at two hour intervals for six doses. It was also noted in this series that about half as many

[The following text is extremely faint and illegible due to extreme contrast and noise. It appears to be a series of handwritten lines, possibly a list or a narrative, covering the majority of the page.]

operations and comparable forms of anesthesia, but given a preventive course of neostigmine injections (1 cc of 1:4000 solution immediately after the operation and repeated every two hours for six doses), only two, or 4 per cent, had to be catheterized postoperatively, the remaining forty-eight patients voided without difficulty within ten hours after operation. Another series of thirty-five patients was given 1 cc of neostigmine, of 1:2000 solution, only after there was evidence of urinary retention, twenty-three, or 66 per cent of this group, voided within one hour after injection.

Neostigmine has been advocated as helpful in the expulsion of *ureteral calculi* in conditions in which surgical intervention does not seem warranted and also where manipulative procedures had been unsuccessful in dislodging the stone.¹¹ There is apparently no objection to this use provided constriction of the ureter below the calculi is ruled out.

Although neostigmine stimulates bladder contraction and appears to be an effective means of correcting urinary retention, certain basic facts regarding this problem should not be overlooked. Residual urine, even as small as 3 or 4 ounces, should be avoided. Even though the patient voids in response to neostigmine or otherwise, there is no assurance that a residual amount may not be present unless the patient is catheterized. Inasmuch as catheterization is essential to rule out retention, this measure in itself may make the use of neostigmine unnecessary.

Neostigmine, however, when used for this purpose is safe except where urethral obstruction may be present as a result of prostatic hypertrophy or other causes.

Myasthenia Gravis.—In 1934, Dr. Mary Walker,¹³ who at a medical conference had been told that physostigmine neutralized the effects of curare and that myasthenia gravis was similar to curare poisoning, deduced that physostigmine would be of benefit in myasthenia gravis. Her original paper, describing the effects of physostigmine in three cases of myasthenia gravis, is a monumental contribution to the medical history of this disease. After trying physostigmine successfully, Dr. Walker, with Dr. Pritchard, used neostigmine injections in this same condition with even better results because physostigmine had been rather toxic. Her paper, which was published in 1934, spread this knowledge throughout the world.

Neostigmine was first used in myasthenia gravis in the United States in 1935, in the historic Ether Dome of the Massachusetts General Hospital, Boston, where a patient with this disease was given injection of this drug with alleviation of her symptoms. In 1936, ¹⁴ first used oral neostigmine in the form of neostigmine bromide, 15 mg per tablet, in the treatment of myasthenia gravis. From time on, as more and more cases of myasthenia gravis were recog-

nized and were brought to the attention of the clinicians, this drug became increasingly valuable in the treatment of the condition.

At first, the dosage was conservative, three, four or five tablets per day being given. For example, in the clinic at the Massachusetts General Hospital, during 1936, 1937 and 1938,¹⁵ the average dosage of oral neostigmine was between five and seven tablets per day. Then, as more severe cases were brought to the attention of the physicians and more courage and experience in handling the disease with oral neostigmine were developed, the daily dosage began to be increased,

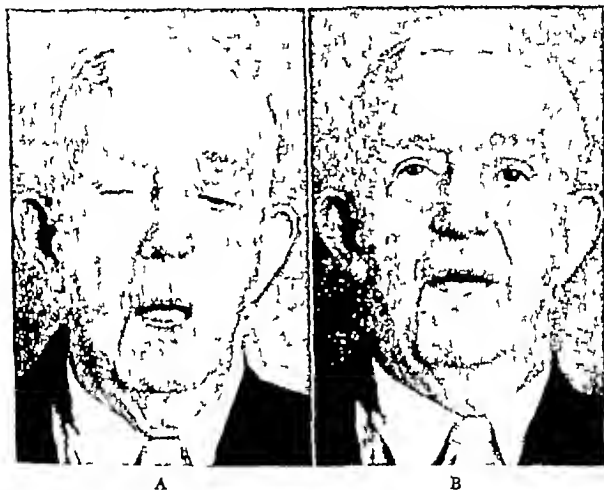


Fig 200—A, A case of myasthenia gravis before neostigmine injection. B, Same patient after neostigmine injection.

so that it was not considered unusual in 1939 for patients to be taking from twelve to fourteen tablets a day and, in rare cases, as many as twenty tablets per day. As complications from overdosage with oral medicine were better understood and the need for adequate treatment in severe cases was seen, the dosage has been increased to as much as twenty five to thirty oral tablets per day in severe cases. The average, however, taking for example 100 cases at the Massachusetts General Hospital Myasthenia Clinic in 1946, remained around ten tablets per day, and it is to be emphasized that the higher dosage must be given with great care and under constant supervision because

neostigmine is a dangerous drug in these amounts. If frequent supervision of the dosage is insisted on and readjustments according to the *individual needs of each patient* are watched carefully, 85 per cent can be carried satisfactorily on oral medication.

Neostigmine as a Diagnostic Test in Myasthenia Gravis—In 1935, Schwab and Viets were impressed with the remarkably clear and definite response of myasthenia patients to the intramuscular injection of neostigmine methylsulfate (15 mg), as opposed to the lack of response to the drug in patients not suffering from myasthenia. They therefore devised a test which is known as the *neostigmine test*,¹⁸ which consists of the injection of 1.5 mg of neostigmine methylsulfate, with 0.6 mg of atropine sulfate to prevent hypermotility of the intestinal tract. A diagnostic test ampule containing these amounts of neostigmine and atropine in 1 cc of sterile water is available. This test has had wide application and has been used in a variety of ways and is accepted as one of the best ways of establishing the presence of myasthenia gravis. The most objective method of judging the results of the test is to note the effect of the neostigmine on the degree of ptosis, amount of dysphagia, strength of grip, ability to chew, strength of voice, or some exercise such as lifting a book over the head or climbing stairs. More elaborate and exact testing can be done by making ergograms and electromyograms, by studying the fluoroscopic appearance of a barium swallow, by studies of photographs (still or movies) or by records of the voice on a disk. All of these procedures should be carried out both before and fifteen to twenty minutes after neostigmine injection.

The test has been negative 180 times in a variety of neuromuscular diseases listed in Table 2.

Ephedrine sulfate, grain $\frac{3}{8}$ (24 mg) three times a day, somewhat augments the effect of neostigmine in myasthenia. Guanidine hydrochloride, 65 to 125 mg, three or four times daily, and potassium chloride or gluconate, 500 mg three times a day, are useful in a few patients.

Other Neuromuscular Disorders.—Since myasthenia gravis is a neuromuscular disease, presumably a disturbance at the myoneural junction, it was thought early that neostigmine might benefit other neuromuscular diseases.

In *progressive muscular dystrophy*, neostigmine has been used by a variety of observers in different forms and in different amounts, and the general impression is that it is without benefit. In *neuritis*, *nerve injuries* and *infectious polyneuritis*, the use of neostigmine is not useful. It has been used in various concentrations and forms in *paralysis agitans*, and has been found to have no specific value, but it often has a favorable secondary effect on the dry mouth and constipation due to the use of large amounts of atropine. Furthermore,

the mild and sustained vasodilating effect of neostigmine in small doses is reported to be of benefit in some patients. Controlled experiments, using placebo drugs, have failed to show that neostigmine produces any objective improvement. The slight subjective benefit sometimes reported is probably due entirely to the secondary effects of the drug mentioned above.

There has been a large literature, stimulated by Kabat's reports,¹⁷ on the specific benefit of neostigmine in *spastic states*, particularly in spastic birth injuries. Clinical reports of the failure of neostigmine to benefit the *spastic states* are not found in the medical literature. There are, however, a number of orthopedic centers, notably in New York, Chicago, Boston, and St. Louis, where it has been tried and given up. However, one of us (R.S.S.), in a small series of twelve

TABLE 2

DISEASES WITH NEGATIVE NEOSTIGMINE TESTS (TWELVE YEARS)

	No of Cases
Progressive muscular dystrophy	15
Progressive muscular atrophy*	10
Multiple sclerosis	15
Psychoneurosis	50
Progressive ophthalmoplegia	10
Tabes dorsalis	8
Cerebral infarcts	15
Poliomyelitis	10
Peripheral neuritis	20
Bell's palsy	7
Parkinson's disease	12
Miscellaneous	8
Total	160

* The drug makes fibrillations worse and should be used with great care in this disease. See Case III.

cases carefully controlled and subjected to ergographic, electromyographic and neurological studies, found no objective improvement in the spastic state resulting from birth injuries with paralysis in older people with hemiplegias, or in isolated cases of injury to tumor where only one limb was involved. In these experiments placebo injections served as a control, and physiotherapy and other general measures were excluded. The same results can be obtained in cases of athetosis, paralysis agitans, dystonia musculorum deformans and other conditions involving the pyramidal and extrapyramidal systems.

Neostigmine has been tried in various forms of rheumatoid arthritis, osteoarthritis and traumatic arthritis and the impression of those workers (Balboni et al.¹⁸) was that it had no effect.

jective and careful in their conclusions is that the drug is of little value, except for the secondary effects of neostigmine described before

Neostigmine has been used in *poliomyelitis*, in both acute and chronic cases. When the drug is evaluated and controlled against placebos, massage and physiotherapy are excluded as contributing factors, and vasodilating effects checked against hot packs or radiant heat, the conclusion is that neostigmine is of little value in this condition.¹⁹ Since neostigmine injections produce a sustained vasodilating effect for several hours, patients with *poliomyelitis* who *report benefit from hot packs or radiant heat* might logically be expected to do well on this drug. This would be important if facilities for continuous physical therapy are not available and as a supplement to such treatment.

In summary, therefore, excluding myasthenia gravis, neostigmine, except for the *secondary effects*, is of little specific value in neuromuscular disorders as a group.

Pregnancy Test.—Neostigmine, because of its specific effect on smooth muscles and also because of its vasodilating properties, can stimulate the uterus to contractions. In pregnant women, however, the effect of neostigmine on the uterus is minimal, and no ill effect on the gravid uterus has been noted. In fact, Viets and associates showed that pregnant patients with myasthenia gravis can take large amounts of the drug with no ill effect.²⁰ Therefore, if an injection of 1 mg of neostigmine is given to a person who is thought to be pregnant and menstruation occurs within a few hours or one or two days, it is a normal response to an inhibited menstruation, by psychic or other means, whereas if an actual pregnancy existed, no response would have been forthcoming. This test is specific and has been used with success by a number of investigators.²¹

Neostigmine as a Vasodilator.—Perlow²² has shown that as little as 0.5 mg of neostigmine will cause a 2 to 3 degree rise in skin temperature in normal persons and a more marked (4 to 5 degree) and prolonged (five to six hours) one in vasospastics (Raynaud's disease, etc.). This is of practical value in these states, particularly as a sustained effect over many hours is not possible with other methods and sympathetic surgery is not always indicated. With oral tablets (one 15 mg tablet, three or four times daily) a good response is usually obtained (thirty-one cases). Persons upset by this amount take one-half tablet (7.5 mg).

Neostigmine as a vasodilator in atrophic rhinitis is advocated by Kun²³ and also by Henner²⁴ who show that it is less upsetting than trogens or mecholyl. They used a nasal spray of the 1:2000 solution, limiting the volume in each nostril to 0.25 cc (0.125 mg) three to four times daily. No side effects were noted.

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is not discussed. In cases of Parkinson's disease where the patient is taking a large amount of atropine drugs, the beneficial effect of neostigmine may result from two possible pharmacological actions, to wit (1) the neutralization of the unpleasant sequelae of atropine on the intestinal tract and the glandular secretions and, (2) the dilating effect on the blood vessels in the periphery. Both of these effects are definite and desirable and, if intended and understood, make the use of this drug under these circumstances perfectly warranted and reasonable. A great many patients with such chronic neurological disorders complain of cold extremities especially at night. Mild vasodilation throughout the day would make them *feel better* even if it had no specific effect on the disease. Small doses of neostigmine can do this as well as combat constipation (a complaint of most chronic invalids). The dose should be started small enough to avoid *all* unpleasant side effects and given often enough so that the effect is sustained throughout the day. For example, 75 mg (one-half tablet) three to five times daily would be a typical dose.

It should be pointed out again that morphine by its depressant effect on secretions in the stomach and the reduction of the motility in part of the stomach—the so-called *constipating effect of morphine*—is partially neutralized by neostigmine, and, therefore, the drug may well benefit a patient taking morphine, particularly in large amounts. This is particularly true in patients with carcinomatosis and other fatal diseases requiring large and repeated amounts of morphine, demerol and other narcotics over long periods. These drugs not only cause constipation but because of their inhibiting effect on the secretions, with resultant dryness of the mouth, produce a tendency to aerophagia and thus cause distention. The use of small amounts of neostigmine in these cases either by injection of 1 to 2 cc three times a day or by the administration of 1 or 2 oral tablets a day relieves some of this distention, gastric atony and intestinal stasis by stimulating the passage of flatus and bowel movements. Therefore, such patients are considerably more comfortable and relieved. This is a perfectly reasonable and intelligent pharmacological use of this drug in these conditions, and a clinician, when faced with this problem, can often render the patient more comfortable and easy by this means.

Since myasthenia gravis is closely similar to curare poisoning in its appearance, neostigmine was found to be a specific antidote for curare. This is important because of the increasing use of curare intravenously, intramuscularly in various conditions involving muscular spasm. Curare is used with the electric shock therapy for psychoses as a preparation for fractures during the convulsion. Whenever curare is used, whether intravenously or intramuscularly, the dangerous conditions that might develop from overdosage or sensitivity to the drug can be neutralized promptly by slow intravenous injection of neostigmine.

methylsulfate, 0.5 mg to as high as 1 mg., according to the amount of curare that it is necessary to neutralize Neostigmine should be available and ready for instant use whenever curare is given and the presence of this specific antidote will make the use of curare safer

CLINICAL EXAMPLES OF THE USE OF NEOSTIGMINE

Case I Myasthenia Gravis

A 68 year old lawyer had complained for two years of ptosis of both lids which developed in the afternoon, a marked sense of fatigue and occasional difficulty in chewing and swallowing. He had been treated by an ophthalmologist and by his doctor with tonic and diet, without improvement.

Intramuscular injection of 1.5 mg. of neostigmine methylsulfate with 0.6 mg. of atropine sulfate caused the ptosis and the double vision to disappear in about fifteen minutes. The patient was then able to chew meat and swallow without difficulty and no longer complained of fatigue. He was given a trial dosage of six tablets of neostigmine bromide (15 mg.) daily spaced at regular intervals. After some adjustment of the dosage, he was able to return to his law practice. He has carried on without any difficulty for the past six years, the amount of neostigmine required varying from seven to nine tablets a day.

The beneficial effect of the drug was clear and specific and the objective findings of disappearance of the ptosis and restored ability to chew and swallow his food were striking and clear-cut. During the first years use of neostigmine bromide, the patient was given twenty tablets of a placebo mixture appearing exactly like neostigmine. His wife was informed of the purpose of the test. About 24 hours after taking the first doses, the patient quite angrily telephoned that the medicine was no good, the effect had been lost, and the ptosis and general weakness had promptly returned.

Here, substitution of a placebo tablet clearly confirmed the specific effect of the neostigmine on this condition.

Case II. Progressive Muscular Dystrophy

A patient with progressive muscular dystrophy of eight years duration, with considerable loss of muscle substance in his thighs and upper arms and with the disability in his gait characteristic of the disease, came to the Myasthenia Clinic in the hope of getting help. He was put on oral neostigmine bromide, four to five tablets during the day, and at the end of the week reported that he felt better, particularly in walking. There was no objective change noted.

During the second week the patient was given a placebo tablet which was similar in appearance to the neostigmine bromide tablet. At the end of the second week he reported that he felt even better than the first week, as the cramps and the occasional diarrhea the first medicine had produced had disappeared.

It was obvious that this patient intensely desired some help and by pure suggestion and faith in the doctor, and in the medicine, was fooled into believing he was better.

Case III Progressive Muscular Atrophy

A patient with amyotrophic lateral sclerosis, 63 years old suffering from fibrillations of the tongue atrophy of the tongue muscles fibrillations in the shoulders and arms and marked dysphagia, was admitted to the Hospital in 1935 with the idea that neostigmine might benefit him. The diagnostic dose of 1.5 mg. of neo-

stigmine methylsulfate plus 0.6 mg of atropine sulfate was given him. Twenty minutes later the fibrillations in the tongue had more than doubled and gross fasciculations had spread from the shoulders down into both extremities and into the hands. Ten minutes later they were over the entire body and were very distressing to the patient. A few minutes later severe dyspnea had developed and the patient had become cyanotic, he was in great distress, especially as he felt a sensation of impending death. An intravenous injection of 0.6 mg of atropine sulfate restored him to a satisfactory state, and in another hour he was out of danger.

Neostigmine in progressive muscular atrophy is definitely contraindicated, even in mild cases.

Case IV. Paralysis Agitans

A woman of 45, with a two year history of bilateral paralysis agitans, with a marked tremor and definite rigidity on both sides of her body, had been receiving hyoscine hydrobromide, 0.6 mg four or five times a day, with some improvement in her condition. She had read of the effect of neostigmine in a lay journal and came to the Clinic to receive this particular medication. Before the injection of neostigmine the severity of her tremor was carefully observed clinically and by the electromyogram and the degree of rigidity assessed by means of the electromyogram integrator and the usual neurological observations. After an injection of 1.5 mg of neostigmine methylsulfate, with 0.6 mg of atropine sulfate, the same quantitative observations were repeated. There was no observable effect on either the tremor, the amount of rigidity or the amount of voluntary muscle power of this patient, nor was there any subjective improvement from the drug. She persuaded us, however, to prescribe four 15 mg tablets of neostigmine daily. The patient reported in two weeks that she felt somewhat better. The disagreeable dryness in her mouth that she had previously noted was lessened, and her bowels, which had been constipated for years, had been moving twice daily, which she felt was a great triumph. She felt that both her hands and feet felt somewhat warmer during the night than previously, a complaint which had bothered her. There was no objective change in the parkinsonism, her tremor, or her rigidity. Since the drug apparently was making this patient happier, it was continued.

Case V. Congenital Spasticity

A 14 year old girl with congenital spasticity, with definite, typical deformity of both feet, an awkward, spastic gait, speech impediment and some evidence of mental impairment (her I.Q. being around 65) came from Canada for the purpose of trying neostigmine, having read in a lay journal that it was effective in her condition. She was carefully studied in the laboratory as to the range of motion and muscle strength. Electromyograms showing the amount of spasticity and rigidity were made and a thorough base line was obtained. After the injection of diagnostic ampules of neostigmine (1.5 mg neostigmine methylsulfate, plus 0.6 mg atropine sulfate), these same quantitative studies were repeated in the course of two hours. There was no demonstrable effect on the gait, the muscle strength, the rigidity, the amount of speech impediment or in the patient's subjective report.

the next week, she was put on four tablets of oral neostigmine bromide daily.

She was observed in the hospital very carefully for any evidence of improvement. None

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for the next three weeks neostigmine was omitted and the patient was given intensive physiotherapy, muscle education, exercises, massage, heat and some occupational training. At the end of a month there was questionable evidence of improvement in both her speech and gait. This was only slight and the objective

tests with the electromyogram and other quantitative measurements failed to show improvement. The patient and her family felt that she was definitely improved with this treatment and planned to continue it.

It is quite clear that, in this particular case, the neostigmine had no benefit, yet had it been continued along with the physiotherapeutic measures, it might have been assumed that the drug was benefiting this particular individual.

Case VI Terminal Cancer

The patient, 71 years old, was suffering from terminal cancer of the pancreas and was receiving every two hours 2 to 3 cc. of demerol hydrochloride to relieve the pain, in addition to codeine by mouth and, occasionally, intramuscular morphine sulfate. She was greatly troubled by distention, excessive dryness of the mouth and inability to pass either flatus or feces. Hot turpentine stupes and the usual enemas were not effective. Neostigmine methylsulfate was used cautiously at first, in 0.5 mg. doses intramuscularly, later increased to 1 mg., twice a day, with excellent results as to the passage of flatus or feces. There was some reduction in the dryness of the mouth. The patient subjectively reported that she felt greatly improved. The tense tympanitic abdomen was significantly reduced and this form of medication was continued until death, with good results for the period of three weeks that it was used.

Some surgeons feel that with gastric suction, as with a Wangensteen apparatus, the need for neostigmine can be avoided. In small hospitals or those caring for many chronic cases, where such equipment and the staff to set it up and care for it are not available, and last but not least, in the home, the use of a drug is more convenient and preferred by both patient and relatives.

Case VII Poliomyelitis

A 19 year old soldier was admitted to a military hospital in the Pacific (where one of the authors was on duty) three weeks after the onset of poliomyelitis, which involved one arm and both legs. The patient had been receiving neostigmine therapy, four tablets of 15 mg. each daily, beginning four days after the onset of the illness. For the past two weeks, he had been complaining of a diarrhea, four or five times a day, cramps, excessive salivation, and disagreeable, excessive sweating. The amount of paralysis was carefully examined and the amount of pain in his muscles noted, and the neostigmine was withdrawn. The diarrhea stopped within twenty four hours, and the disagreeable, excessive sweating disappeared. There was no change in the tenderness of the muscles or in the paralysis.

In this particular case, since it was in the tropics, with a high humidity, vasodilatation of the extremities was probably maximal, and the neostigmine effect on the blood vessels was unnecessary and undesirable and its stimulating effect on the intestinal tract was a sequel that was also undesirable. No rationale for the use of this particular drug could be seen and the patient's progress from then on without neostigmine was quite satisfactory.

Case VIII. Peripheral Nerve Paralysis

A 32 year old patient, with a complete left seventh nerve paralysis of one week's duration, came into the Clinic for muscle testing and evaluation. His left eye was red and painful and bothered him a great deal. The electrical test and examination showed a complete left seventh paralysis with no electrical reactions present. At the suggestion of one of the medical students, who had been reading about the effect of neostigmine on peripheral nerve regeneration, this patient was given neostigmine bromide, four tablets of 15 mg each, daily, and was asked to return in two weeks. When he reported, the eye condition had completely cleared up but there was no change in the facial paralysis, which was still complete, both by electrical reaction and clinical condition. The effect of the neostigmine, as the patient described it, was to increase the lacrimal secretion significantly and to cause disappearance of the eye symptoms within two days. When the patient was seen two months later, he had experienced about 50 per cent relief of his facial paralysis.

Case IX. Psychoneurosis

An obese, flabby, middle-aged woman of 52 was referred to the hospital with the diagnosis of myasthenia gravis. Her history was one of fatigue in the morning for the past twenty years, accompanied by a variety of complaints that included headache, excessive belching of gas, severe constipation, irritability and insomnia. There were none of the characteristic findings of myasthenia gravis as the history was taken and, indeed, there were no objective findings of fatigability of any of the muscles of the body. Her general picture was that of a mild hypochondriac with some depression and fatigue, both of which followed her menopause. The diagnosis of myasthenia gravis had been made in a small hospital near her home. Six tablets of neostigmine bromide per day had been prescribed. The fatigability had persisted in spite of the neostigmine, and it was for this reason that she had been referred to our hospital. The persistent symptoms of constipation and excessive belching of air had been somewhat relieved and she felt, she said, a little better as a result of the medicine, but her awareness of the excessive peristaltic rumbling, and the excessive saliva in her mouth bothered her a little. A diagnostic study with neostigmine failed to show any myasthenic responses at all, as one might have expected. Neostigmine was discontinued and the patient was given a better diet. With the reasonable use of cathartics and some psychotherapy, she improved tremendously.

Comment.—From the above cases, it is to be seen that neostigmine is most effective in myasthenia-gravis, where it is a specific form of therapy, unequaled by any other compound known at this time. It is effective, with prompt results, in various forms of intestinal atony and postoperative or drug-induced distention of the abdomen. In a variety of neuromuscular and other conditions, *it exerts secondary favorable effects by dilating peripheral vessels, stimulating the gastrointestinal tract and neutralizing the unpleasant side effects of the opium drugs and the constipating effects of morphine and demerol.*

The secondary effects of neostigmine account for most of the favorable subjective reports of its value. They are real, based on sound pharmacology, and should not be neglected by the physician whose interest is to make his patient as happy and comfortable as he can.

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CLINICAL USES OF HISTAMINE AND HISTAMINASE— AN EVALUATION

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HISTAMINE is β -iminazolyethylamine and may be produced by the decarboxylation of the amino acid histidine. It is present in varying concentrations throughout the body tissues and has a wide variety of actions. The drug is rapidly absorbed after parenteral administration, iontophoresis, and from the under surface of the tongue but apparently is not effective when given by mouth. Histamine causes capillary and arteriolar dilation in man and a transient fall which is followed by a slight temporary elevation in blood pressure. A marked increase in the amount and acidity of the gastric secretions occurs. Constriction of the bronchioles may be produced by a direct action on smooth muscle. The reaction of the vascular system is short lived indicating that the drug is rapidly destroyed or inactivated, possibly by deamination with subsequent oxidation.¹ Histaminase, an enzyme which is present in the body tissues, destroys histamine more slowly. The liberation of epinephrine, which has a marked ability to counteract the effects of histamine, probably is also an important mechanism of protection against the drug.

Histamine is available for diagnostic or therapeutic use as histamine phosphate and histamine dihydrochloride. We have used histamine acid phosphate[†] in 1 cc. ampules which contain 1 mg. of histamine base and in 5 cc. rubber capped bottles which contain 0.2 mg. of the base per cubic centimeter. Allergic individuals, especially those with asthma or the history of asthma, may have alarming reactions after the parenteral administration of histamine. These reactions should be prevented by a careful history but if they do occur the prompt intramuscular administration of 0.4 cc. of 1:1000 epinephrine usually will relieve the distress. If epinephrine is not available a tourniquet should be placed above the site of injection in order to retard further absorption of the drug.

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HISTAMINE AS A DIAGNOSTIC AGENT

Test of Gastric Function.—Histamine is chiefly employed to make the diagnosis of complete achlorhydria when analysis of the fasting stomach contents reveals the absence of free hydrochloric acid. A dose of 0.25 to 0.50 mg of histamine base is given subcutaneously in the upper extremity. Twenty minutes after the injection the gastric contents are again removed and examined. A failure of hydrochloric acid response within a two hour period, provided a systemic reaction to the histamine was observed, indicates permanent achlorhydria. Fractional analyses may be performed by withdrawing and examining the stomach contents every ten to fifteen minutes after the injection of histamine. In normal subjects the initial rise in acidity is followed by a return to normal in sixty to ninety minutes. Some authors have felt that an unusually high rise or a slow fall in acidity was indicative of peptic ulcer but too much reliance cannot be placed on this finding. Likewise, a normal response does not exclude the diagnosis of peptic ulcer. Rivers, Osterberg and Vanzant² demonstrated that a second injection of histamine produced a similar rise and fall in acidity in the majority of subjects studied by means of fractional analyses. This type of test, referred to as the "double histamine test," is of value in studying the effect of antihistamine agents on the gastric response to histamine.

Test for Pheochromocytoma.—Hyman and Mencher³ noted that the administration of histamine in patients with pheochromocytoma would provoke the occurrence of signs and symptoms similar to spontaneous attacks of the disease. It was later suggested by Roth and Kvale⁴ that the intravenous injection of 0.025 or 0.05 mg of histamine base might be useful as a diagnostic test by inducing attacks of paroxysmal hypertension in patients suspected of having a pheochromocytoma. These authors were able to show in three cases of pheochromocytoma that signs and symptoms similar to spontaneous attacks could be induced by histamine injections. Moreover, the blood pressure rose approximately 100 mm of mercury more in response to histamine than the elevation due to the cold pressor tests. In patients with essential arterial hypertension and in normal subjects, on the other hand, the rise in pressure resulting from similar doses of histamine was less than the elevation due to the cold pressor test. The reaction to histamine in these patients with pheochromocytoma is presumably due to the liberation of an epinephrine-like substance from the tumor.

ss The results suggest that under careful observation the use of
 11 for this purpose may be of value

Diagnostic Test for Asthma.—Studies in our laboratory^{5, 6} have indicated that a great many patients with asthma or the history of asthma develop "asthmatic-like" attacks, with a reduction in vital capacity, after the intravenous injection of 0.01 to 0.04 mg of histamine base. It is suggested that such a response might be confirma-

tory evidence of the disease if malingering or hysteria was suspected. A positive response is not specific since patients with bronchitis and emphysema may react in a similar manner.

Circulatory Tests.—The reaction time of the injection of 0.001 mg or less of histamine acid phosphate per kilogram (2.2 pounds) of body weight between the site of intravenous injection and the vessels of the face has been used as a measure of the velocity of blood flow.⁷ In normal subjects the average reaction time measured 23 seconds whereas in congestive heart failure the average was 47 seconds. In our studies the occurrence of a sour or gaseous taste in the mouth after the intravenous injection of 0.02 to 0.04 mg of histamine base furnished a sharper end point.⁸ However, the test is not of great value as a measurement of circulatory velocity because it produces severe reactions in patients with asthma, bronchitis and emphysema. It is in this very group that one would like to use the test, on occasion, to determine the early presence of congestive heart failure.

The flare which develops about the initial red reaction due to the intradermal injection of histamine depends upon adequate local arteriolar circulation and intact peripheral nerves. Presuming that the axon reflex is intact, the absence of a flare after the intradermal injection of 0.1 cc. of 1:1000 histamine acid phosphate means that the local arteriolar circulation in the skin is poor. This may be of importance, for example, in establishing the site for amputation of an extremity.

Evaluation of Peripheral Nerve Lesions.—The absence of a histamine flare may also be used to demonstrate the presence of neurological disturbances presuming that the arteriolar circulation is normal. In 1938 Loeser⁹ reviewed the work done in this field in the light of his own experiences. As little as 0.01 cc of 1:1000 histamine hydrochloride was injected intradermally with a fine hypodermic needle and a tuberculin syringe. Injections were made from 1 to 3 inches (2.5 to 7.5 cm) apart across the area to be tested. Section of the nerve at any point from the spinal ganglia to the skin would abolish the flare after sufficient time had elapsed to allow the nerve to degenerate. Thus the test is of value in determining the presence of degeneration and the rate of regeneration in peripheral nerves following injury and in differentiating hysterical from organic anesthesia. It is helpful as an additional aid in localization of spinal cord lesions and in the differentiation of nerve root from spinal cord involvement. During the recent war, confirmation of these findings was obtained and the simplicity of this type of study reemphasized.¹⁰

THERAPEUTIC USES OF HISTAMINE

Since histamine is found in various body tissues and exerts a profound effect when administered parenterally, it is not surprising that the drug has been considered an etiological agent in a wide variety of diseases. In the acute allergic reaction, for example, it is believed

that histamine is released as a result of damage to cells containing histamine and that the clinical picture which follows is due to the action of histamine. Furthermore the parenteral administration of histamine may produce an exacerbation of the signs and symptoms of certain allergic diseases. The details of some of these problems have been recently reviewed^{11, 12}

Influenced by these theories many attempts have been made, in a variety of diseases, to increase the tolerance to histamine by the parenteral administration of repeated doses of the drug. Unfortunately the term "desensitization" has often been incorrectly applied to this procedure. The mechanism by which increased tolerance may be produced is not clear. It could be explained by a more rapid inactivation of histamine due in part perhaps to a more copious or more facile liberation of epinephrine. It has been ascribed to an increase in tissue histaminase but this has not been demonstrated nor does it seem likely. Best and McHenry¹³ were unable to demonstrate any increase in histaminase in the kidneys of animals given histamine for a period of some weeks. It should be pointed out that in studying the problem of tolerance attention should be directed to more than one type of histamine response since there is evidence to show that tissue response to histamine varies in different parts of the body. Experimental studies in animals have resulted in conflicting reports on the development of resistance to the action of histamine. Relatively few physiological studies have been made in man. In the majority of reports the relief of subjective symptoms, presumed due to histamine, has constituted the major evidence of a decreased reactivity to the drug after a course of histamine therapy.

Varying degrees of success have been reported after the use of histamine in a number of diseases and these are briefly outlined.

Hay Fever and Asthma.—In small amounts histamine has been recommended in the treatment of hay fever and asthma. In the latter condition Dautrebande¹⁴ has demonstrated that small amounts of histamine improve the respiratory pattern whereas larger amounts of the drug make it worse. Presumably this improvement with small doses is due to the more dominant effect of released epinephrine. There would appear to be little need of this type of therapy since sympathomimetic amines may be directly prescribed.

Histamine Cephalgia, Migraine, Ménière's Disease and Multiple Sclerosis.—Horton¹⁵ has reported remarkable success with histamine therapy in the treatment of "histamine cephalgia," a syndrome which has been described as specifically due to histamine release. These results are difficult to interpret since no control cases were included in the study. Relief of symptoms also occurred when histaminase was given, although it is now known that the available preparations of this substance have no clinical value. Thomas and Butler¹⁶ have been impressed by the results of histamine therapy in the treatment of mi-

graine. Atkinson¹⁷ recommends histamine, among other agents, in the treatment of Ménière's disease. There are conflicting reports on the value of histamine in the treatment of multiple sclerosis¹⁸

In these diseases two types of histamine therapy have been employed. In one procedure a solution of histamine diphosphate is used of which 1 cc. is equivalent to 0.1 mg. of histamine base. All injections are given subcutaneously twice a day. The first dose is 0.25 cc. of the solution and with each subsequent injection the dose is increased by 0.05 cc. until an amount of 1 cc. is reached. Patients are then given 1 cc. twice daily for a total period of ten to twenty-one days and following this they receive a maintenance dose of 1 cc. one to three times weekly. Occasionally no maintenance dose is required. If flushing or subjective or objective response to the drug is noted the dosage is reduced 50 per cent and then gradually increased again. Another method of administering the drug for purposes of therapy is by the continuous intravenous injection of a solution of 1 mg. of histamine base as histamine acid phosphate diluted in 500 cc. of isotonic sodium chloride. From three to five injections are given usually on successive days. The administration is begun slowly starting with a rate of 5 drops a minute and if possible increasing to 30 to 40 drops a minute. The total time required for the injection varies and may require only three to four hours. Side reactions may be relieved by slowing the rate or by the administration of 0.4 cc. 1:1000 epinephrine subcutaneously. Precaution should be taken to exclude patients who have asthma or a history of asthma. Administration of antacid preparations is advisable after therapy is completed to counteract the sharp increase in gastric acidity.

Arthritis.—Histamine has been administered to patients with rheumatoid arthritis¹⁹ by subcutaneous injection, iontophoresis and in the form of an ointment. Increase in mobility and relief of pain have been reported, but in the majority of cases histamine has been used only as an adjunct in therapy. Its action is nonspecific and it appears that the application of heat and other methods of counterirritation are equally effective and more easily administered.

In summary, at the present time the therapeutic use of histamine is not recommended. More carefully controlled studies are needed before its use may finally be evaluated.

HISTAMINASE

In 1930 Best and McHenry²⁰ studied a substance to which they gave the name histaminase. It has the properties of an enzyme which slowly inactivates histamine *in vitro* and furnishes an important method for the *in vitro* determination of the presence of histamine. When the enzyme was made commercially available it was enthusiastically employed in the therapy of a wide variety of diseases in which histamine was thought to be an etiological factor. The early

promising reports on treatment were not confirmed and in 1940 Best and McHenry stated "our investigations over a period of ten years have failed to show that the intravenous or intramuscular administration of histaminase has any effect upon histamine present in the body or that given by injection" This problem has recently been reviewed by Feinberg¹¹ in a report to the Council on Pharmacy and Chemistry. In substance he states that there is no valid evidence that the histaminase which is available to date is effective in the treatment of allergic states or diseases in man

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DENGUE FEVER

BRUCE WEBSTER, M D •

DENGUE fever has long been sporadic in certain southern portions of the United States. World War II, occurring as it did in areas where dengue is both endemic and highly epidemic, afforded an opportunity to many physicians to further their knowledge of this disease, and as a consequence, some changes in our clinical concepts of the disease have taken place. Lumley and Taylor¹ and Simmons² have fully outlined our knowledge of the disease to 1943.

Dengue is usually defined as an acute febrile disease of tropical and subtropical areas, caused by a filterable virus, transmitted by mosquitoes and characterized by paroxysms of fever, aches and pains in the joints and muscles, leukopenia and variable rashes. Such a loosely defined clinical entity, without definite readily available means of laboratory diagnosis, is subject to wide variation in interpretation and consequent differential diagnosis. Some observers laid down too rigid criteria for the diagnosis of dengue and many atypical cases were recorded as "fevers of unknown origin." On the other hand, in a few instances, the diagnosis may have been made without adequate supporting evidence. It would appear to be the general impression that the number of cases of dengue fever reported in our armed forces represents the minimal rather than the maximal number who may have had the disease.

INCIDENCE

In the United States armed forces the highest incidence of dengue occurred in the southwest Pacific, the China-Burma-India and the Pacific Ocean areas. In all theaters there was a tendency for the admission rate to decrease as the war progressed. This is compatible with improved mosquito control and a growing awareness on the part of line and medical officers of the importance of dengue as a problem.

The epidemic nature of dengue fever was readily apparent when one observed any detailed survey of hospital admission rates in the various theaters. Epidemics commonly occurred immediately or shortly after occupation of an area formerly held by the enemy. Typical of

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these was an epidemic reported in a Pacific island during the summer of 1944. In four weeks the admission rate for dengue rose to 3500 per thousand troops per annum. At the end of this time active mosquito control measures were instituted. Shell casings, empty tins and other debris capable of affording breeding places were cleaned up. The whole island was subjected to D D T. airplane spraying on two occasions and hand spraying of living quarters was carried out. On the eighteenth day after the first spraying, the admissions decreased rapidly. A new unit which entered the area ten days after the first spraying remained free from dengue.

The effectiveness of removal of mosquito breeding areas and D D T spraying was further illustrated in an epidemic that occurred in a hospital center in New Guinea in December 1944 and January 1945. During early December the admission rate for dengue rose rapidly to 1700/1000. On December 14 an active campaign was directed toward clearing underbrush and tin can dumps in the area. Airplane spraying with D D T was carried out on December 14 and December 30. No appreciable change in admission rate was noted until December 29 or approximately two weeks after the first spraying. At that time the admission rate fell to 525/1000. By January 26 the rate had fallen to 0/1000. Mosquito counts indicated a decrease of 75 to 80 per cent in adults.

ETIOLOGY

The common mosquito vectors usually associated with dengue fever were incriminated in the various epidemics of World War II. *Aedes albopictus* (*Stegomyia scutellaris*) was predominant in the New Guinea Area. In another epidemic in 1945 *Culex quinque fasciatus* were present in large numbers while *Aedes albopictus*, although widely scattered, were of low density. Nevertheless, epidemiological studies of the distribution of cases appeared to indicate that *Aedes albopictus* was the vector—in spite of the low density.

CLINICAL CHARACTERISTICS

Since no simple laboratory test exists for the identification of dengue, the specific diagnosis of an individual case may be difficult. Furthermore, epidemics vary widely in severity and duration of symptoms. In consequence, the clinical accounts of the various epidemics vary widely.

Incubation Period.—Information obtained as a result of D D T spraying and from the movement of new troops into an epidemic indicates that the incubation period was approximately ten days, variants ranging from five to fourteen days. The onset was usually sudden. LeRoy and Lindberg³ felt that the severity of onset usually indicated the severity of the course.

Fever—In an epidemic of 350 cases in the Pacific area, typical "saddle back" fever was noted in 50 per cent of the cases. In addition 25 per cent had a fairly typical fever and the remaining 25 per cent were atypical.

Pain—Headache and postorbital pain were common symptoms of onset. Approximately 60 per cent of cases complained of pain in the limbs or back. While these symptoms were moderately severe, they would not seem to warrant the old term of "break-bone fever."

Rash—The consistency with which typical rashes occurred in the various epidemics of dengue appeared to have a direct relationship to the severity of the symptoms. In one epidemic a rash was noted on the third to the seventh day in 50 per cent of the cases. It lasted thirty six to forty-eight hours. Rashes were noted in 50 per cent of the cases in another epidemic. In the milder epidemics rashes were not noted or were of a transient nature, lasting only eighteen to twenty four hours. Since a terminal rash was noted in only 85 per cent of Simmons's experimentally induced cases,² the widespread opinion that rashes are a constant characteristic sign must be modified.

Changes in Blood Cells—That leukocyte changes, especially leukopenia, occur in the majority of patients at some time during the course of dengue fever has long been recognized. Professor Alexander Murphy of the University of Brisbane, who has had long clinical experience with dengue fever, is of the opinion that these changes are the most important diagnostic criteria of the disease.⁴ Simmons² has summarized the white blood cell changes in his series of cases as follows:

1. All of the patients developed leukopenia.
2. The total leukopenia usually began on the second day and progressed to a low point of about 2000 cells on the fourth or fifth day after onset. The counts returned to normal several days later than did the temperature.
3. The leukopenia was produced by a decrease in both the mononuclear and mature neutrophilic polymorphonuclear cells.
4. Coincident with this decrease in mature cells, there was a marked increase in the immature granulocytes. The "shift to the left" was a constant reaction.

In general, the various observers commenting on the blood picture confirmed these changes. LeRoy and Lindberg³ described a white blood cell count ranging from 2100 to 7400 cells per cu. mm. The average was 4630. They noted a steady decrease in granulocytes to at least 30 to 40 per cent of normal. They noted also vacuolization of monocytes. The marked neutropenia and relative lymphocytosis continued during convalescence. Toxic irritation cells were noted also during convalescence. A leukopenia caused by a decrease in granulocytes was present in 56 per cent of the cases. In another series of 350 cases it was found that 71.8 per cent had white blood cell counts

below 5000 There was a relative increase in lymphocytes to over 40 per cent in half of the cases

The apparent inconsistencies in the blood picture in these cases can perhaps best be explained by the fact that, in the majority of cases, only one white blood cell count was recorded and this was usually taken early in the disease. In the more carefully studied cases, Simmons's findings were almost universally confirmed

Miscellaneous Signs and Symptoms.—The cervical or inguinal lymph glands were enlarged in a large percentage of cases Orchitis occurred in 6 per cent of one series of cases Blood in the seminal fluid during convalescence was described⁵ Epistaxis was a rare symptom Jaundice was noted in 2 per cent of the cases in one epidemic Since infectious hepatitis was present in this area at this time, the possibility of intercurrent infectious jaundice would seem likely

Convalescence.—Marked physical asthenia and mental depression have been discussed by the majority of writers when describing dengue fever These symptoms would appear to vary widely with the degree of severity of the disease Whereas it was often absent in the milder atypical cases, it was almost a universal accompaniment of the severe variety

Dengue-like Fevers.—There appeared to be a hesitancy on the part of many physicians to make the diagnosis of dengue, even during an epidemic, unless all of the classical signs and symptoms were present It has been pointed out by Simmons² and others that, even in experimentally produced cases, considerable variation in the clinical course occurs As a result of this conservative attitude toward making the diagnosis of dengue, numerous accounts of epidemics of "dengue-like" fever have been made Johnson, Martin and Breslow⁶ have described an epidemic of approximately 1000 cases in Okinawa in the summer of 1945 This epidemic began in April and rose gradually to mid-July *Aedes albopictus* were present in low densities The disease was characterized by scanty rashes, variable fevers, some of which were "saddle back," headache, postorbital pain, prostration, increasing leukopenia with progress of the disease in 56 per cent of the cases and a decrease in granulocytes

In various other areas of the Pacific Ocean similar epidemics occurred, mild in nature, often lacking the classical "saddle-back" fever, usually with transient or absent rashes When such cases occurred in the middle of a recognized epidemic, they were regarded usually as dengue If a large series of such cases was studied, enough classical occurred to make the diagnosis definite If one directs attention to the white blood count in the descriptions of most of these atypical epidemics, it would appear that the diagnosis of dengue was justified Laboratory confirmation of these atypical strains as dengue is, of course, necessary Such confirmation was made in at least one epi-

demic However, it would appear that dengue fever is a disease with a widely variable degree of clinical severity and that various strains can produce atypical clinical forms

DIFFERENTIAL DIAGNOSIS

In the absence of readily available means of establishing the specific diagnosis of dengue fever, reliance must be placed on a combination of epidemiological, clinical and laboratory evidence The diseases which are most likely to lead to confusion are influenza, sand fly fever, Rift Valley fever, cerebrospinal meningitis, rubella, measles and scarlet fever Important as it is to establish the diagnosis of dengue, still more so is it to avoid the calamity of overlooking some more serious disease by calling it dengue

Many cases of dengue were unquestionably lost in the diagnosis of "fever undiagnosed" This is especially true of epidemics of atypical dengue in which observers restricted the diagnosis to classical examples of the disease The high admission rates for "fever undiagnosed" in areas where dengue is epidemic would appear to be significant in this regard

TREATMENT

The various observers of dengue epidemics during World War II have refrained from writing about treatment. This may be indicative of the fact that symptomatic treatment was of little avail It would appear that bed rest and adequate fluids are the essential factors in the treatment of this disease From the standpoint of prevention, it is essential that patients be screened twenty-four hours a day to prevent the spread of the epidemic Adequate convalescence is necessary because of the debilitating effect of many strains of dengue

IMMUNITY

On clinical, epidemiological and experimental evidence, it would appear that the characteristics of dengue immunity may be described as follows

- a Immunity may be evanescent, lasting weeks only, or prolonged, lasting years
- b It may be partial or absolute
- c One attack tends to confer a short immunity, repeated attacks tend to increase the durability of this immunity
- d Subsequent attacks tend to be milder
- e Residents of epidemic areas exhibit some degree of immunity
- f The immunity conferred by an attack is highly individual or variable

PREVENTION

The frequency with which epidemics occurred in newly occupied areas or in areas in which mosquito control was poor was clearly

demonstrated in World War II. The tendency of *Aedes aegypti* to breed in clean, still water makes discarded shell cases, tin cans, bottles and similar refuse potential breeding spots. The early elimination of all such hazards, together with proper mosquito control discipline as concerns clothing, bed nets and the use of repellents, will go a long way toward preventing an epidemic. In the presence of an epidemic, DDT by airplane and ground spraying will result in a marked drop in admission rates ten days later.

Sabin and his associates⁷ have reported the propagation of dengue virus by intracerebral inoculation in mice and the subsequent use of this modified virus as a vaccine for the production of immunity against dengue. The use of such a vaccine on a wide scale in endemic areas would appear to have great future possibilities.

SUMMARY

1 Dengue fever was a relatively common disease in our armed forces in the Southwest Pacific, the China-Burma-India and the Pacific Ocean areas.

2 The incidence in these areas tended to decrease sharply with successive years of the war because of improved methods of control.

3 Individual epidemics could be checked in from ten to twenty days by control of mosquito breeding areas, including ground and airplane DDT spraying.

4 The clinical signs and symptoms showed wide variation in severity in different epidemics. All of the classical manifestations were not always present.

5 "Dengue-like" fevers were described. In many of these epidemics, a review of the data would appear to indicate that a diagnosis of dengue was justified.

6 The development of a leukopenia with a decrease in both the mononuclear and mature neutrophilic polymorphonuclear cells appeared to be a constant finding in dengue fever. This was accompanied by an increase in immature granulocytes.

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PRACTICAL ASPECTS OF EPILEPSY

(With Special Consideration of Epilepsy in Children)

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GENERAL CONSIDERATIONS

We consider epilepsy as a disorder of function of the brain manifested by recurring attacks of dimmed or completely lost consciousness, accompanied by release phenomena, usually motor. As a rule, there is a corresponding alteration of brain-wave pattern.¹ Epileptic fits are believed to be due to sudden and involuntary explosions of groups of neurons, most frequently of the motor cortex, even though the etiology behind these discharges varies from case to case. Cobb² enumerated a list of sixty or more conditions which may be accompanied by epileptic discharges. The more important ones are organic lesions of the brain such as scars, tumors, syphilis, abscess, poor supply of oxygen, disturbances of the acid-base equilibrium (especially in the form of alkalosis), changes of extra- and intraneuronal constituents (hypoglycemia, hypocalcemia), disturbances of water balance, disturbances of intracranial pressure or of intracranial blood flow (Best and Taylor).³

At present it is customary to subdivide the numerous individual causes into two major groups—the idiopathic and the organic. The term, idiopathic, or like labels such as essential, cryptic, genetic (Lennox), is applied to that large group of patients whose primary difficulty is attacks and who show no cause for them. The designation—organic, symptomatic, acquired—applies to those patients whose seizures are secondary to some structural or physiological disturbance. These terms, idiopathic and symptomatic, are useful designations but not necessarily final or even mutually exclusive—for an acquired or symptomatic epilepsy may develop upon a genetic tendency. The distinction is of some value at this time in the practical direction of treatment.

ETIOLOGICAL CONSIDERATIONS

Lennox and Gibbs⁴ reported that 60 per cent of the parents, siblings and children of epileptic patients have an abnormal pattern in their

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electroencephalograms This fact does not make them clinically manifest epileptics, to be sure, but is an indication of a tendency

Clinical studies, on the other hand, do not shed a definite light on the problem of *inheritance* in epilepsy Myerson,⁵ in a study of 1000 epileptics, was able to uncover epilepsy in other members of the immediate family in only four cases Gowers,⁶ however, found 27.3 per cent "inherited" epilepsy in a series of 2400 epileptics However great the clinical discrepancies reported are, we agree thoroughly with Bing⁷ that individuals with epileptic heredity who did not suffer from attacks up to the age of 21 probably will never develop "idiopathic" epilepsy One of us (J.L.F.) in an experience of twenty-five years has found "inherited" epilepsy uncommon

Epilepsy is in all probability never transmitted, although the tendency to a lowered convulsive threshold may very well be Why this threshold is lower in some children than in others cannot be satisfactorily explained To speak of "latent epileptiform" tendencies in a child with electroencephalographic abnormalities is incorrect The young sister of one of our epileptic patients was found to have a grossly abnormal brain-wave pattern, this child suffered later from a severe pneumonia, accompanied by high temperatures, yet no seizures ever developed!

Considering *etiological classifications*, we should recall that convulsions occurring in the first two decades of life are commonly due to "idiopathic" epilepsy (McEachern)⁸ Those occurring in the next two decades should lead our investigations more to a suspicion of tumor, subdural hematoma, or infectious process, whereas those of later life are frequently associated with cerebrovascular disorders, or cardio-renal diseases

Peterman⁹ has found that up to the age of 1 month acute infections are an infrequent etiologic factor. In contrast, acute infections in the age group between 1 month and 3 years serve as a frequent cause He also states that in the age group from 1 year to 10 years, infection is a fairly common antecedent Peterman⁹ also remarks that scarlatina is the one infectious disease most frequently accompanied by epileptic seizures, others are smallpox, influenza, measles and typhoid fever

It is incorrect to term these seizures "febrile convulsions"—inferring that they necessarily disappear in the future To be sure, a good many do disappear But 15 to 20 per cent of children (Buchanan)¹⁰ who have attacks associated with febrile disease in childhood have spontaneous attacks later in life, in our experience, a "seizure-free" interval between ten to twenty years is not unusual

and similarly O'Neil¹² pointed out recently that 45 per cent of all cases of convulsive disorders in infancy and childhood can, in the present state of diagnostic possibilities be classified only as

"Idiopathic." The highest incidence of these "idiopathic" epilepsies was observed in children between 6 and 16 Crump¹¹ found that during the first year of life cerebral birth injuries and their residues were the most frequent causes. Congenital malformations of the brain are likewise common (porencephaly, microencephaly, etc.) During the ages of 1 to 5 these factors play a less significant role. At this period the role of acute infections (intracranial and extracranial) become more important. The percentage incidence of generalized convulsions found in different disease states in which attacks were prone to occur were as follows:

	Per cent
Tetany	90
Tetanus	89
Meningitis	55
Brain tumors	42
Encephalitis	39
Different types of poisoning	33
Acute glomerular nephritis	20
Cerebral atrophy	13
Head injuries	10
Acute extracranial infections	7

We would like to add here that in our experience children show a higher incidence of so-called post-traumatic epilepsy than adults. Here, as in adults, seizures are more common following penetrating wounds than those which are superficial. We know, of course, ever since the basic studies of Penfield¹² and Foerster, that a meningocerebral cicatrix is capable of precipitating attacks by reason of the pull on adjacent cerebral structures. Cobb¹⁴ has, however, pointed out that heredity plays an important role even in "traumatic" epilepsy as a "pre-disposing" factor.

Contrary to frequently expressed opinion, we would like to state that the incidence of epilepsy in cases of *congenital* lues is low (Menninger),¹⁵ however, acquired lues acts as an important contributing or even precipitating factor in the development of epileptiform seizures in adults. When the first convulsion occurs in adult life think of trauma, tumor and *Treponema pallida*.

TYPES OF SEIZURES

Grand Mal Convulsions—Although some seizures come suddenly without warning they are usually preceded by prodromal symptoms and an "aura" which may not only be visual ("lights," "spots"), auditory ("hissing"), or gustatory, but more frequently visceral ("a strange feeling over the stomach"). Prodromal symptoms are frequently expressed in children by psychic changes, abrupt changes of mood, or dreadful fears. The aura usually lasts for a brief period only and then all goes blank. The patient becomes unconscious. A weird

cry may precede his fall. Then follows the typical generalized tonic-clonic convulsion, the patient's eyes are turned upward, foam accumulates at his mouth, he may bite his tongue and may even wet himself. Although a few patients show an immediate return to consciousness, a delayed return is the rule. We may observe periods of postconvulsive sleep, of stuporous behavior interrupted by automatic activity, as sudden running away, furor states, and the performing of complex but purposeless acts usually in the same sequence, such as making and remaking of beds. After the attack the patient may feel weak, battered, depressed, and may suffer from headache.

The brain-wave pattern during seizure shows large continuous spikes.¹⁶ The electroencephalogram in the seizure-free period shows these typical spiky grand-mal discharges only in 15 to 20 per cent, whereas 60 to 70 per cent of patients afflicted with this type of seizure show various forms of other abnormalities which are usually "in bursts," or paroxysmal.

Petit Mal Epilepsy.—In petit mal epilepsies no major convulsive phenomena are observed. Children especially show a high percentage of nonconvulsive epilepsies. Lennox¹⁷ calls the typical petit mal attack "pyknoepilepsy," meaning a transient lapse of consciousness lasting from 5 to 30 seconds. The parents and relatives of patients afflicted by it speak of "blank spells," "staring attacks," "peculiar daydreaming" and the like. The electroencephalographic abnormalities during such a spell consist of fairly high dart and dome formations, usually in the three per second band. We find this abnormality in 80 per cent of our patients even in the seizure-free period, especially when we ask them to hyperventilate during the brain-wave recording. Only 5 to 10 per cent of "interseizure" records in patients suffering from this type of seizures are normal and about 10 per cent show different types of electroencephalographic abnormalities.

Myoclonic epileptic jerks are also classified by Lennox¹⁷ as belonging to the group of petit mal epilepsies, they are characterized by a single quick contraction of flexor muscles, in many cases, consciousness may not even be dimmed. The brain-wave pattern during one of these contractions shows usually a single dart and dome.

Akinetic epilepsy (Lennox)¹⁷ is characterized by a sudden loss of postural control with a nodding of the head and usually a sudden fall, and belongs also to the petit mal epilepsies. In the electroencephalogram we often observe series of high-voltage spike-dome formations in the 2 per second band, frequently localized. These three types of petit

mal seizures have certain features in common (Lennox)¹⁷ alternate

dome pattern in the electroencephalogram, great frequency, many attacks, abrupt onset and termination, maintenance of mentality and a strong tendency to improvement with age.

Psychomotor Epilepsy.—An attack of psychomotor epilepsy is a

typical epileptic manifestation per se During an attack, the patient shows various degrees of impaired consciousness Unaware of his actions, he may walk for some distance without realization of what is going on and without the ability to recall this act. He may suffer from complex hallucinations and may even perform compulsive acts of a rather complex nature in an automatic fashion Complete or patchy amnesia after the attack is the rule Slight muscular tonic phenomena sometimes accompany these spells The typical electroencephalographic manifestation during such a seizure consists of square-topped slow waves Yet, this pattern is observed in only 50 per cent of these patients in the seizure-free interval, whereas 35 per cent show various forms of slow or fast activities, and 15 per cent show a normal electroencephalographic record

Jacksonian Seizures—H Jackson demonstrated that focal irritation of the motor cortex by vascular, neoplastic or cicatricial lesions may "fire off" a focal attack by jerking in the corresponding region of the peripheral muscles Then appears a "march" of jerking movements according to the cerebrocortical distribution of motor pattern (For example, the attack begins in one finger, spreads to the whole upper extremity, to the mouth, and finally to the foot area) The "march" may be one not only of motor phenomena but of sensation as well We know now that subcortical lesions may irritate motor *fibers* also (not only motor *centers*!) In a typical jacksonian seizure consciousness is retained. A ventriculogram or pneumoencephalogram may be necessary to localize the lesion with certainty An electroencephalogram may show a focus of abnormal frequency over one area, plus a so-called "reversal of phase" over the affected region Subtentorial lesions (posterior fossa), however, cannot be diagnosed as to localization by an electroencephalogram

Although most of the cases of jacksonian epilepsy in children are caused by an abscess, tumor, regional meningitis, aneurysms or scar tissue, in some cases no structural focus can be found.

The site of the lesion is most often in the *motor area*, more rarely in the frontal and parietal regions nearby, or in the anterior part of the temporal lobe (Nielsen)¹⁸ Especially in children we may find a focus at a distance from the motor area in the posterior fossa, giving rise to early clinical manifestations of increased intracranial pressure (choked disk, vomiting, slow pulse, and the like) and causing jacksonian manifestations by intracranial transmission of pressure or venous stasis

Focal Convulsions.—These attacks usually start in a jacksonian-like fashion and may initiate a one-sided convulsion A generalized convulsion usually follows and consciousness is lost The electroencephalogram during the attacks shows the typical high voltage fast waves beginning locally, the record in the seizure free period may

give evidence of a focus for the seizure, again provided the lesion is not located "subtentorially"

It should be mentioned here that in our experience as well as in that of others (Buchanan),¹⁰ children may suffer from a series of localized attacks as the introductory phase before classical major attacks occur. We must witness an actual central "march of jerking" over the limb in order to establish a diagnosis of jacksonian epilepsy in children! Even then neurosurgical interference in children on account of "focal" convulsions without *permanent* localizing neurological signs should be carefully weighed, as the operative findings and results may prove failures.

Status Epilepticus.—Here continuous *grand mal attacks* follow one another in continuous succession, sometimes with brief intervals between. Consciousness is not usually regained, the body temperature rises, the cardiac rate increases, the heart action itself becomes weaker, and even uremic manifestations occur. The child may die from such complications as pneumonia and final cardiorenal failure. Vigorous and prompt therapy is always necessary to save the patient's life.

Assortment of Attacks.—Very few patients present one type of attack only. Indeed, if a patient be followed over a period of years, he will usually exhibit a variety of attacks—*petit mal*, *grand mal*, psychomotor—at different times. An assortment of attacks is the rule.

MEDICINAL THERAPY (GENERAL CONSIDERATIONS)

The aim of treatment is to prevent attacks and to maintain well-being. Experience has shown that certain drugs are capable of reducing the number of attacks even to the point of almost complete freedom. Such drugs, however, produce side actions which may be undesirable and even toxic. Hence proper treatment requires a careful selection and dosage of drugs so as to obtain the maximum benefit with the minimum harm.

The following general principles of medicinal treatment may be considered before we take up specific drugs.

1 The dosage should be adequate. The aim of therapy is not a certain number of capsules daily, but cessation of attacks. Hence, physicians who treat epilepsy successfully do not hesitate to use enough medication. Indeed, one may remark, as an aside, that a certain mail order house owes its success to the use of large doses of anticonvulsant drugs—even though there is produced an occasional toxic reaction. The occurrence of attacks is a command for more therapy.

The dosage must be individualized and adjusted to each particular patient. It is best to start with a small dose and increase the amount in accordance with need. One of us (J.L.F.)¹⁰ had shown that if dilantin sodium be administered in a large dose at first, it is

likely to upset the patient, but if the initial dose be small, and then steadily increased until the attacks are controlled, the patient can better tolerate a larger amount. The value of graduated doses is two-fold sometimes a small dose proves adequate and tolerance to side action is obtained

3 Combinations of drugs are advisable. We have realized that one drug alone may relieve one feature, but not the assortment of attacks so common in epilepsy. Experience has shown that one drug is effective for grand mal but does not alter the petit mal seizures. Furthermore, it is possible to combine two drugs in such a way as to secure an addition of their anticonvulsant value but a subtraction of their side actions. Thus the combination of dilantin sodium and phenobarbital is synergistic in controlling seizures, while phenobarbital sedates the nervousness that dilantin sometimes causes. The therapist may need two to three different medicinal agents to achieve for the patient the goal of freedom from symptoms and relative well-being.

4 Continuity of treatment. As epilepsy is usually a long-term illness, the patient must be instructed as to the need for long care and observation. He should be warned against too early judgment as to success or failure. We have known patients to stop a drug within a day or two after its initial use merely because there was an attack directly after swallowing a pill or capsule. They did not realize that it may take several days or more for a patient to build up a protective level. Indeed, the patient who obtained the most satisfactory result with dilantin had two attacks on the day she first took dilantin, then remained seizure-free for many years.

The patient should be instructed to come frequently at first, then every two weeks or every month until the condition is stabilized and the optimum benefit obtained. Then the visits may be reduced to one every three months—or as needed.

Another practical point is to forewarn the family against the tendency to an abrupt discontinuation of all medication. Patients sometimes stop drugs for what to them are two good reasons—they feel improved or unimproved. Unfortunately the abrupt cessation of anticonvulsant drugs invites status epilepticus. Hence the patient should be instructed to continue medication under supervision as long as necessary. Only after there has been freedom from spells for several years may it be safe to reduce (not cut out) the dosage. Such a reduction should be a cautious tapering off and not a sudden withdrawal. As Putnam²⁰ explained, treatment for epilepsy is like insulin treatment for diabetes—a long term program.

MEDICINAL THERAPY (SPECIFIC DRUGS)

Bromides—For close to 100 years bromides were popular as a remedy in epilepsy. They were used in doses of 5 to 15 grains (0.03

to 0.1 gm.) of sodium bromide twice to four times daily. We begin with the relatively smaller amount and increase as necessary to control attacks.

Unfortunately the effectiveness of bromides was but moderate and the unpleasant side reactions of drowsiness and skin lesions were marked. Hence, bromides have been used less and less as newer and more effective anticonvulsants were introduced. Bromides are still used for their general sedative effect for disturbed institutional epileptics.

Phenobarbital.—Phenobarbital has been a widely used and effective drug in epilepsy. It is valuable in all types of epilepsy, though perhaps more effective in grand mal than in petit mal. It is our practice to start with 0.03 gm. ($\frac{1}{2}$ grain) tablets twice a day for children and 0.1 ($1\frac{1}{2}$ grains) twice a day for adults. Usually it is necessary to increase the amount because the initial dose may not prevent attacks, or as the patient acquires tolerance. Sometimes we go up to a total of 0.2 to 0.3 gm. in children and 0.4 to 0.6 gm. in adults. Obviously the development of drowsiness would be a caution against too great an increase in phenobarbital. Buchanan¹⁰ makes the statement that 10 grains of bromide, $1\frac{1}{2}$ grains of dilantin and $\frac{1}{2}$ grain of phenobarbital are equivalent in their anticonvulsant action.

Dilantin Sodium.—This has proved an outstanding remedy in the relief of grand mal convulsions. The introduction of this drug by Merritt and Putnam¹⁰ marked a distinct epoch in the therapy of epilepsy.

Dilantin sodium, properly administered, will provide considerable relief in the majority of epileptic patients suffering from grand mal attacks, whether these be idiopathic or symptomatic. Unfortunately this drug produces unpleasant side actions such as tremors, restlessness, indigestion, and later swelling of the gums in some patients. Therefore, proper therapy requires the use of dilantin carefully balanced to achieve effect with the minimum of side actions. This is feasible in most instances if one follows the suggestion of a gradual and slow increase in dose as needed. Thus patients acquire a tolerance to the toxic effects and are relatively free of uncomfortable side actions. At the outset it is a mistake to cut off all previous medication abruptly and to give a patient three or four capsules (0.1 gm.) of dilantin daily. Our practice is as follows:

For adults who have not taken any previous medication, we prescribe one $1\frac{1}{2}$ grain capsule (0.1 gm.) of dilantin sodium daily for one week and then two capsules daily for the second week. These can be taken at breakfast and supper. If the patient remains attack-free, the dosage is maintained at two capsules daily. This proved an adequate amount in the case of Miss P. H., who obtained freedom from seizures for over five years, however, most adults are not as

fortunate and require additional medication. We therefore increase the amount to three capsules for the third and fourth weeks. If the attacks persist, then the therapist has the choice of adding one more capsule of dilantin or of supplementing the dilantin sodium with phenobarbital. It is our custom then to add phenobarbital, grains $1\frac{1}{2}$ (0.1 gm) at bedtime and to increase this to two or three tablets daily. Thus some of our adult patients are receiving a total of $4\frac{1}{2}$ grains (0.3 gm) of dilantin sodium and $4\frac{1}{2}$ grains (0.3 gm) of phenobarbital daily. This combination of the two drugs adds their anticonvulsant qualities while each offsets the other's side actions. For phenobarbital provides the sedation which tends to neutralize the irritability caused by dilantin.

In some patients the side actions are severe. There may be skin manifestations, rarely, nervous symptoms of tremors, ataxia, even diplopia can occur, the gums may protrude to the point of interference with chewing. Fortunately such severe symptoms are uncommon unless the dosage be raised to 0.5 or 0.6 gm. To relieve gastric distress, Merritt²² recommends the use of soda bicarbonate with dilantin. For the gum hypertrophy, vitamin C is not indicated, but massage has been advocated. If these difficulties be pronounced, a reduction in dosage is necessary even when the patient has enjoyed benefit from the drug.

The dose for children, according to Merritt, is $4\frac{1}{2}$ to 6 grains (0.3 to 0.4 gm) for those over 12 to 14 years, and in younger children 3 to $4\frac{1}{2}$ grains (0.2 to 0.3 gm) preferably in divided amounts spread over the day. Buchanan¹⁰ advises similar doses.

In patients who have been getting phenobarbital without satisfactory results, we supplement this by dilantin sodium. Phenobarbital is withdrawn *gradually* if it has been causing drowsiness. In all anticonvulsant therapy we make changes gradually so that the transition is smooth.

Tridione *—Tridione was introduced by Lennox,¹⁷ Richards²³ and Perlstein²⁴. It is a new and promising drug for the control of petit mal spells (Lennox)²³. The studies to date indicate its remarkable effectiveness in all varieties of petit mal. We have used this drug in a considerable number of patients, in some of whom the results were conspicuously successful. For instance K. M., a girl of seven, was referred to us because of frequent spells of staring during which her head would turn to the side. The teachers complained of her inattention and her parents scolded her for daydreaming. The initial physical examination proved negative, the psychological studies revealed a well adjusted child, while the electroencephalogram showed typical spike and wave pattern. Tridione was started using three capsules.

* We wish to thank Dr. Richard K. Richards of the Abbott Laboratories for a generous supply of tridione for investigational purposes.

4½ grains (0.3 gm) daily. Within one week this girl obtained a reduction in spells, and in several weeks she became entirely free. She has remained free for many months on a dose of three capsules daily. Our early experience with this child as well as others confirmed Lennox's reports about this drug. Not only did this child obtain relief of spells, but she also became more alert and better behaved. Indeed her mother speaks proudly of her friendly behavior and improved school work.

Tridione is not effective in grand mal nor is it of value in jacksonian attacks. For instance, J. R. had an attack of encephalitis in boyhood and later developed petit mal and jacksonian attacks. The electroencephalogram revealed focal signs in the right motor area, consistent with the march of weakness in the left leg, which ushered in attacks. Tridione was begun and there was apparent reduction in spells. However, after a temporary relief, the attacks recurred with their usual frequency despite large doses of the drug.

Lennox stresses the value of tridione especially in pediatric practice. "the drug is relatively specific for the petit mal triad not helped by other anticonvulsants, the high proportion of relief of the troublesome blackouts or falls which may occur up to 300 and 400 per month." This author suggests the following dosage: "infants, 1 capsule (0.3 gm), children, 2 to 4 years of age, 2 capsules, 5 years and above, 3 capsules. Amounts may be increased to a maximum of three times those named."

The dose which we have employed for adults is one capsule three times a day at the outset, then a steady increase to six or in some cases eight capsules daily.

Tridione has its side actions. Many patients complain of photophobia. When such persons walk from the interior of a house or building to the outdoors, all objects present a bright glare like fresh snow glittering in the winter sunlight. This hypersensitivity (hyperchromopsia) can be relieved by the use of dark glasses.

In some patients a rash may occur. One of our patients, who gave a history of allergy, developed a marked urticarial rash, but as a rule this is uncommon. An even less frequent but more serious complication is the development of agranulocytic anemia. Two fatalities from such anemias have been reported.^{26, 27}

One must use tridione, therefore, with caution and check the blood picture at intervals. Indeed, because of this hazard, tridione might better be reserved for patients with frequent petit mal spells.

Further experience has diminished our enthusiasm for the use of drug. For the adult patient whose petit mal attacks are infrequent, we would hesitate to prescribe tridione. For the youngster troubled by many petit mal spells tridione carefully given may be a truly effective

remedy. Even the brain-wave pattern has shown a distinct improvement in some of our cases, again particularly in children.

Mesantoin*—This new drug, introduced by Kozol²⁸ and by Loscalzo,²⁹ has been reported as highly effective in treating grand mal epilepsies. Our experience confirms the favorable results of Kozol. We have added mesantoin to dilantin sodium and to phenobarbital, or have used it alone. Our dosage for adults is $1\frac{1}{2}$ grain (0.1 gm.) tablets twice daily for one week, then steadily increased over a period of weeks in accordance with need. Kozol has prescribed as high as ten tablets a day in severe cases. He recommends 0.4 gm. as the average daily dose for a child and 0.6 gm. for youths and adults.

We have employed mesantoin in some forty patients for about twelve months and have found it an effective remedy to date. Thus far we have encountered few, if any, side actions other than the tendency to drowsiness when larger amounts are given. Certainly the therapeutic efficacy is in some cases as great as that of dilantin. Some patients unrelieved by dilantin have enjoyed a striking freedom from attacks by the addition to or replacement of dilantin by mesantoin, and do not show tremors or gum swelling.

For example, B. V., a woman of 30, required five capsules of dilantin to get any substantial help in the control of her seizures. At this dose she was relatively free of spells but complained of unsteadiness in walking and showed considerable gum hypertrophy. Mesantoin was prescribed in June, 1946, replacing two capsules of dilantin sodium with two tablets of mesantoin. She is now taking three tablets of mesantoin and two capsules of dilantin sodium. She is free of spells and entirely free of ataxia. Even the swelling of the gums has receded. Another patient, S. J., with a severe form of organic epilepsy, who had previously stopped all medication, was given mesantoin, one tablet three times a day, on July 1, 1946. As he continued to have occasional attacks, the dose was steadily increased to five tablets daily. For the past few months he has been attack-free and reports a grand feeling of well being.

Thus far mesantoin rivals dilantin sodium as a remedy for the control of grand mal attacks of epilepsy. Yet it is too early to compare its efficacy with that of dilantin as an anticonvulsant drug though one can emphasize the relative freedom from toxic side actions. Its major sphere of influence in our experience is as a supplementary drug. Many patients have been taking two to four capsules of dilantin sodium daily with some improvement, yet attacks continue. If the

* We wish to thank Mr. S. M. Fessel of the Sandoz Chemical Works, Inc., as well as Dr. M. D. Friedman, Associate Director of The Neuropsychiatric Institute of Cleveland, through whom a generous supply of this drug was made available to us.

dosage of dilantin is raised to a more effective anticonvulsant level the patient is likely to become irritable, sleepless and tremulous. However, if mesantoin is added to dilantin, the effectiveness is distinctly raised while the toxic action is diminished. We would caution against the hasty withdrawal of dilantin or phenobarbital when these drugs are only partially effective and their replacement by mesantoin. As yet, for some unexplained reason, the new drug does not seem to take over the function of replacement at first. The body does not tolerate the withdrawal of the earlier drug and a recurrence of attacks is apt to develop. Hence, if the other remedies are not completely effective, add mesantoin and at a later date reduce the dosage cautiously.

We agree with Kozol's²⁸ remark about conservatism in the use of a new preparation, but one cannot but feel optimistic about this new drug. Its side actions, in addition to drowsiness, are the tendency to a skin rash. This is usually slight and transitory. The drowsiness has not been disabling but if large doses of mesantoin are used we have prescribed dextrodine sulfate. Dextrodine sulfate in 5 mg doses at breakfast and lunch restores alertness without decreasing the therapeutic value of mesantoin.

Other Drugs.—Glutamic acid was tried several years ago for petit mal,³⁰ but the large dose necessary and its unsustained therapeutic value make it a drug of doubtful worth.

DIETOTHERAPY

It has been known that acidosis tends to reduce, while alkalosis increases, the tendency to attacks. As a consequence, ketogenic diets were introduced. They enjoyed a certain vogue in children. However, the work involved in the preparation, the unpleasantness of the diet, and its limited therapeutic value have led to its gradual disuse.

For a time, a limited water intake or dehydration was recommended. This caused great discomfort and little, if any, improvement. It has long been discarded.

It is our practice to encourage a normal, well-balanced diet for our epileptic patients. Of course, if a particular individual is allergic to and distressed by some article of food, common sense would lead to an avoidance of it.

SURGICAL THERAPY

Penfield and Erickson's³¹ book gives a clear picture of the status of surgery in some forms of epilepsy. Patients whose attacks are caused by a brain tumor obviously should undergo surgery. The cases of traumatic epilepsy in whom there is a focal trigger mechanism have been treated with good results. Recently, Walker³² and his colleagues have carried out an extensive program for the help of the brain-injured.

soldier They have found that surgery can benefit such patients, however, not only the traumatic scar but the epileptogenous brain tissue surrounding the scar should be removed After surgery is done, anti convulsant therapy is still in order

PSYCHOTHERAPY

As a supplement to anticonvulsant medication, the doctor can help the patient and the family along several lines which we may cover under the heading of psychotherapy

Adjustment to the Concept of the Disease—From time immemorial epilepsy has connoted evil spirits, demoniacal possession, deterioration. Yet epilepsy is a sickness for which there is hope and often useful therapy Many epileptics can maintain their places in the world of normal average beings One need not compliment the patient with the historical statement that Mahomet and Byron and Napoleon and Dostoevski were epileptics True, it makes some patients feel better to be thus identified with the world's great figures It is more important, however, to stress the modern contributions of Paskind, Lennox, Fetterman, that many epileptics have average I Q's and maintain them throughout a lifetime Recently one of us (J L F) re examined by psychometric tests patients whose I Q's were measured twenty years ago, and found that those rechecked did not show deterioration! One must free the family and the patient of antiquated notions about this illness

As regards the epileptic child, we would encourage the parents to hope for a spontaneous remission for a longer or shorter period Though this is uncommon, it does occur often enough to hold out this hope. Next, the parents should not overprotect the child beyond the needs of safety We recall one child whose parents kept him at home all the time because of fear of bodily injury We feel there is more injury to the child's ego if he be kept imprisoned and overprotected than if he be allowed to participate in most activities It is advisable to encourage the companionship of pals or buddies, who may be instructed secretly to keep a watchful eye for possible mishaps

Education—The education of the epileptic child should be continued. In certain communities a pupil who has had seizures in the classroom is expelled from school. This is an injustice The fellow pupils should be instructed by the school physician about the possibility of a faint or a fit in any of the children and to meet such occurrence with poise and not with hysteria. Life cannot be made shockproof—and childhood is not too early to learn this Where a school refuses to allow a pupil's return, then the board of education should provide a special school (such as Detroit has) or should furnish a tutor We recently saw a girl of 10 who could not read or write because she had been expelled from the first grade of school

after she had some attacks in class. We insisted upon the need for her education and she is now being tutored at home.

Vocational Training.—The vocational training of an epileptic child must reckon with the probability of a continuance of attacks and the hazards involved. If a child shows any interest whatsoever in gardening and farming, this should be encouraged. Our experience indicates that an epileptic is best off working for himself in some occupation which is not too hazardous. Farming is one of the best for those who do not show special talents along any other specific line. The parents of an epileptic child must pay special attention to his aptitudes and guide them into a channel of later industrial usefulness.

The adult epileptic of course should be kept employed. Some succeed in finding suitable jobs (watch repair, key making, bookkeeping, accounting). They should avoid work on railroads and jobs that entail climbing ladders such as roofing. So too, traveling salesmen run a risk—unless their attacks have been checked.

For those epileptics who are unemployable the community should create a sheltered workshop such as the Auracraft project⁸⁸ which we have set up in Cleveland. Here epileptics otherwise unemployable are able to keep busy at safe, yet remunerative, work.

Social Problems.—Among the social problems that adult epileptics face are those of marriage and raising children. These problems do not have a perfect answer. The decision depends upon the intelligence and personality of the individual and his partner rather than upon the epilepsy alone. If a person is normal except for his attacks and the person he loves is also normal, there should be no objection to marriage and the raising of a family.

TREATMENT OF STATUS EPILEPTICUS

Status epilepticus can often be prevented by instructing the patient to avoid an abrupt withdrawal of anticonvulsant medication. If this state does occur, it may be cleared in many instances by the prompt use of sodium phenobarbital, 2 to 8 grams, intramuscularly or intravenously. If this medication proves insufficient, then sodium amytal or paraldehyde intravenously, or even ether anesthesia, may be used.

CONCLUSIONS

1. Epilepsy is a chronic disease manifested clinically by attacks of diminution or loss of consciousness and released visceral and motor phenomena. These clinical symptoms are attended by alterations in brain waves, dysrhythmia. The changes in the brain-wave pattern reflect, to a certain degree, the type of spell—petit mal, grand mal, jacksonian or psychomotor. As a rule, patients exhibit an assortment of attacks.

2 The symptoms of epilepsy can now be reduced or eliminated in a large majority of patients by the use of specific medication

3 Bromides, phenobarbital, dilantin sodium, tridione and mesantoin are now available as effective drugs in epilepsy

4 These drugs may be used alone or in combination

5 The aim of drug therapy is the control of attacks and not any fixed dosage of medication. One should not hesitate to employ an adequate dosage, within the limitations of possible toxic side actions

6 A gradually increasing dosage of medication in accordance with need is best tolerated. Avoid starting with large doses and caution against abrupt withdrawal of anticonvulsant drugs

7 Combinations of phenobarbital and dilantin sodium are often effective in grand mal attacks

8 Tridione is a new and effective drug in petit mal spells, but its worth has been lessened by its potential toxicity

9 Mesantoin is a new and promising drug in grand mal, thus far it has proved to be an effective anticonvulsant remedy. It may be used alone or in combination with dilantin sodium. Its side actions are slight.

10 As a supplement to anticonvulsant medication, the epileptic needs guidance toward a healthy adjustment to the illness, to vocational usefulness, and towards social happiness

We can subscribe to Lennox's²³ hopeful attitude as to the gains in epilepsy when he states "From the caveman to bromide, many thousand of years, from bromide to phenobarbital, seventy-five years, from phenobarbital to diphenylhydantoin, twenty five years, from diphenylhydantoin to trimethyloxazolidine-2, 4-dione, eight years. At this threefold rate of acceleration, we should have yet another effective remedy by the spring of 1948!"

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MANAGEMENT OF CHRONIC CONGESTIVE HEART FAILURE

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The management of chronic heart failure has been well established. yet there are many clinical problems arising at the bedside which require clarification. For instance (1) Should patients with chronic heart failure be kept at bed rest for long periods? (2) How often should mercurials be given? (3) Is digitalis effective in the presence of sinus rhythm and heart failure? (4) May fluids be given freely? These questions should be reconsidered in the light of the dynamic mechanisms established for heart failure and of the pharmacodynamics of digitalis, the xanthine diuretics, the acidifying salts and the mercurials.

In approaching these problems we propose, where possible, to lay down criteria for the treatment of chronic congestive heart failure predicated upon established physiological concepts. The treatment should be such that it may be carried out in the home just as efficiently as at the hospital.

MECHANISM OF CONGESTIVE HEART FAILURE

The mechanism of heart failure is failure of either the left or right ventricle or both to propel a normal minute volume of blood, causing an increase in back pressure in the left auricle and the pulmonary veins or the tributaries of the superior and inferior venae cavae. Forward failure caused by a low cardiac output and low renal blood flow is less important than back pressure in the chronic phase, except for chronic adhesive pericarditis.

In left ventricular failure the pulmonary vascular bed is increased so that less air space remains and a more rigid lung results causing dyspnea. Pulmonary capillary pressure rises. Simultaneously the stimulation of the vagal endings causes tachypnea by the Hering-Breuer reflex. These factors may produce a disturbance in exchange of gases and cause anoxemia of the capillary walls. Simultaneously the rigid lung impairs lymphatic drainage. As a result the alveolar walls are damaged and exudation of fluid into the alveoli follows.

In right ventricular failure the lesser circulation shows hypertension, the right ventricle is enlarged, the blood volume in the systemic veins is increased, the plasma volume is increased, the liver is en-

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larged, the viscera are engorged and edema of the lower extremities follows, along with fluid in serous cavities. When liver congestion is present for a long period, portal hypertension follows and the clinical picture of cardiac cirrhosis is found.

Various reflex mechanisms combine to offset the impending failure of the ventricles. These are the reflexes mediated through the vasomotor centers which cause increased coronary blood flow in the normal heart. These reflexes are initiated by (1) changes in aortic pressure, (2) increase in heart rate and (3) reflex vasomotor control arising in the aorta, carotid sinus and heart. When the adaptive mechanisms are no longer sufficient to offset the failure of the ventricle, dilatation of the ventricular fibers occurs. This mechanism was elaborated by Starling and his co-workers who found that the work of the heart and the oxygen consumption bore a linear relationship to diastolic fiber length. They showed that exposure of a larger chemical surface by dilatation enabled the heart to set free greater physical energy and in this way increase the minute volume.

It is evident that dilatation is not at this time a pernicious process, since it is the only means whereby a heart working against increased resistance, the effects of inflammation or valvular defects, may continue to function adequately. Moreover, dilatation over a prolonged period of time leads to hypertrophy. Thus the association of hypertrophy with some degree of dilatation is a fairly constant one in the diseased heart.

However, hypertrophy like dilatation also causes mechanical disadvantages. Unless the heart rate is slow, diffusion of blood must be less in the thick than in the normal fiber because of shortened diastole. Harrison and his co-workers have shown that pulse rates are in inverse ratio to the thickness of the fiber of the animal heart. The nutrition becomes diminished in the thickened fiber which sooner or later develops anoxemia.

To maintain cardiac efficiency, recurring phases of dilatation and hypertrophy must occur. With greater dilatation there is relatively less mechanical efficiency, and more oxygen consumed per unit of work, thus, dilatation becomes a pernicious process when it no longer leads to further hypertrophy and results in irreversible cardiac failure.

Short bouts of tachycardia may cause progressive dilatation and failure in an enlarged compensated heart, although a normal heart can tolerate prolonged tachycardia. In the large heart, the burden of impairment of coronary flow from thrombosis or sclerosis of a coronary vessel may result in chronic unyielding congestive failure. In

a heart cardiac infarction may be the direct result of the impairment of coronary flow rather than occlusion of a coronary vessel, and failure occurs because of the ischemic infarction superimposed upon chronic coronary insufficiency. In the small heart coronary vascular

episodes may produce few clinical signs and little muscle damage when the collateral circulation is adequate, and failure does not occur.

The kidney function is important since the diuretics act either by increasing glomerular filtration or by decreasing tubular reabsorption, supplementing the action of digitalis in increasing cardiac output. The kidney also diminishes the sodium chloride output in congestive failure. This may be due to the diminished renal flow, a direct selective action during filtration or possibly a direct hormonal action on the sodium excretion.

CASE REPORTS

The following case reports illustrate the application of the physiological concepts in the management of chronic congestive heart failure.

CASE I. Control of Failure by Mercury When Digitalis Failed.—O. P., aged 67 years, an engineer, was disabled because of distress, eructations after meals and sleeplessness. Dyspnea and neck vein distention were evident, the heart was normal in size and sounds, with regular rhythm, a rate of 80, and a soft systolic murmur over the apex. The blood pressure was 150/90. Few rales were present at both lung bases. The liver edge was palpable 1 fingerbreadth below the costal border. No peripheral edema was present. One cubic centimeter of mercurpurin given intravenously caused a diuresis of 3 liters. That night the patient slept well for the first time in months. Digitalis was also given—a total of 1.2 gm. in three days. However, on the third day he again complained of sleeplessness and gas eructations. The lungs were clear. One cubic centimeter of mercurpurin was given and his complaints again subsided. A daily dose of 0.1 gm. of digitalis was then given.

The diet was salt poor and the fluids were limited to 1500 cc. When the patient's weight was 155 pounds or less there was no dyspnea, at 157 pounds he complained of a sense of heaviness and "depression" in the chest, and when above this level he had mild attacks of paroxysmal nocturnal dyspnea. When mercurials were given before the critical weight level was reached, paroxysmal dyspnea did not recur.

This case demonstrates (1) that despite the adequate dosage of digitalis and fluid and salt restriction heart failure persisted, (2) that the administration of mercurials was the only effective method for control of the congestive heart failure, and (3) that attacks of left ventricular failure could be prevented by giving mercurials before the critical weight level was reached.

CASE II. Hypertension, Acute Myocardial Infarction and Paroxysmal Dyspnea Following Cardiac Infarction.—A. R., aged 50 with known hypertension for one year, developed acute myocardial infarction on February 22, 1943 for which he was hospitalized for five weeks. Early in April 1943 he complained of wheezing respirations and on April 19 and 20 he had attacks of paroxysmal nocturnal dyspnea. Examination the next day showed a dyspneic patient, the heart enlarged to the left, the point of maximum impulse outside the midclavicular line in the fifth interspace, sinus rhythm with an apical gallop and the aortic second sound equal to P₂, the blood pressure 120/80, moist rales present over both lung bases, the liver edge 1 fingerbreadth below the costal border and no edema. Electro-

cardiogram showed regular sinus rhythm, left axis deviation, $R_{2,3}$ low voltage, $R-T_1$ and $R-T_4$ elevated, T_1 low and $T-CF_4$ inverted

Since digitalis had been taken daily for several weeks, mercupurin was given and repeated after three days and again after ten days. Digitalis 0.1 gm once daily was continued and ammonium chloride 4 gm was given daily. The rales and dyspnea disappeared, the patient improved and on July 13 he resumed mild activities. The blood pressure varied from 130/80 to 160/100. He remained comfortable and at work taking digitalis and a salt-poor diet until April 26, 1944 when the liver edge was again palpable and the fourth dose of mercupurin was given. The gallop rhythm persisted, the blood pressure varied from 150 to 160 to 104/110. Fluoroscopy showed enlargement of the left ventricle and paradoxical pulsation in the supra-apical area.

This case demonstrates (1) the value of the mercurials in the relief of paroxysmal dyspnea following acute cardiac infarction, and (2) the use of these drugs especially when digitalis no longer controls failure adequately.

CASE III The Subsidence of Left Ventricular Insufficiency and Failure Following More Frequent Administration of Mercurials—R. G., a 46 year old housewife, was treated at the Lebanon Hospital in February 1943 for repeated attacks of pulmonary edema associated with mitral stenosis and auricular fibrillation. She improved after treatment with digitalis, bed rest and occasional mercurials, but attacks of paroxysmal dyspnea soon recurred. Examination at home two months later showed orthopnea, cyanosis, neck vein distention, mitral stenosis and insufficiency, bilateral pleural effusions, the liver edge at the navel and ascites. A salt-poor fluid-restricted diet, digitalis 0.1 gm and ammonium chloride 3 gm daily were prescribed. Mercurials were given twice at two day intervals and then continued at four to five day intervals. Three months later she became semi-ambulatory and returned to her household duties. The interval between mercurials was then increased to five to seven days, but it was noted that increasing dyspnea occurred on the sixth day. The interval was then reduced to five days with marked improvement. For a short period the patient complained of nausea and vomiting the day following the administration of the mercurial, and when bigeminy was once found, digitalis was omitted the day of the mercurial injection and the nausea no longer recurred.

This case demonstrates (1) that more frequent administration of mercurials is necessary so as to keep the patient more comfortable and to avoid increasing dyspnea, and (2) that pulmonary congestion and secondary pulmonary fibrosis which contributes to dyspnea are reduced by mercurials, and (3) that digitalis toxemia is prone to develop on the day the mercurial is given since digitalis is mobilized from the excess fluid drawn from the tissues. It is advisable, therefore, to omit digitalis on the day the mercurial is given especially when the ventricular rate is slow.

CASE IV Acute Pulmonary Edema Following the Onset of Paroxysmal Auricular Fibrillation, and Return to Sinus Rhythm and Cardiac Compensation after the Use of Quinidine after Digitalis Failed—M. G., a 39 year old shipping clerk had chorea at 10 years of age and no serious ailments until he was 39 years of age when he complained of palpitation, pain in the chest and difficulty in

breathing followed by frothy expectoration. Morphine $\frac{1}{2}$ grain was given subcutaneously, 500 cc. of blood was withdrawn from the antecubital vein and oxygen was administered. The patient was digitalized with two doses of 0.5 gm. each given in several hours followed by 0.1 gm. each day for two months.

The shortness of breath and palpitation continued and the patient remained at home. Examination showed mitral stenosis and insufficiency, auricular fibrillation with the ventricular rate varying from 100 to 120 per minute, blood pressure 130/80, and no signs of congestive heart failure. To control the increased ventricular rate digitalis 0.7 gm. was given and the ventricular rate fell to 70 to 80 per minute, but there was no improvement in dyspnea. He was then treated with 3 grains of quinidine every two hours until 72 grains had been taken and the heart rhythm became regular. Three grains was now continued three times each day and the heaviness in the chest and the dyspnea disappeared. The drug was discontinued after several weeks but the irregularity returned so that a second course had to be given to restore regular rhythm. Quinidine is now being taken in dosage of 6 to 9 grains each day and the rhythm remains regular. The patient is now working as a shipping clerk in a department store and finds no difficulty carrying on normal activities.

This case demonstrates (1) the development of heart failure following the onset of auricular fibrillation with a rapid ventricular rate, (2) the failure of digitalis to effectively compensate the heart failure, (3) the effectiveness of quinidine in restoring sinus rhythm and compensation. It is likely that with earlier dehydration the pulmonary congestion would have lessened, anoxia diminished, the work of the heart reduced, and the patient returned sooner to a useful occupation.

CASE V. Failure Induced by Increase in Blood Volume in a Case of Anemia Following Transfusion.—An elderly housewife repeatedly transfused because of an aplastic anemia complained of increasing dyspnea during and immediately after transfusion. Digitalis did not relieve the complaint but mercurials given three to four hours before the transfusion aborted the episodes of dyspnea. When the hemoglobin rose to 7.5 gm. dyspnea became less and transfusion could be given without previous mercurial.

It is interesting to note that while the blood volume is elevated during the early period of diuresis, this increment from 500 cc. of blood which had previously caused dyspnea was tolerated without symptoms when given immediately after diuresis. Evidently the mechanism which aborted the dyspnea was the reduction of the pulmonary congestion from the mercurial.

CASE VI. Chronic Advanced Congestive Heart Failure Complicated by Renal Insufficiency.—E. C., a 72 year old housewife was treated at the Morrisania Hospital in January 1939 for pulmonary edema following myocardial infarction. On bed rest, salt and fluid restriction she improved and was discharged. Two months later she showed mild orthopnea, neck vein distention, an enlarged heart, auricular fibrillation with a ventricular rate of 90 per minute, blood pressure 230/110 moist rales at both lung bases, and liver edge palpable 2 fingerbreadths below the costal border. Digitalis 0.1 gm. daily ammonium chloride 2 gm. three times a day with a salt poor and a fluid restricted diet were continued. Mercurial injection was given and repeated at five to seven day intervals during the next six weeks. The orthopnea and pulmonary and hepatic congestion disappeared and she soon returned to her household duties and discontinued treatment.

The patient was well until November 14 1939 when she again had dyspnea and pulmonary congestion. Fluids again were restricted and 1 gm. of digitalis was

given followed by 0.1 gm each day. She again discontinued therapy against advice but remained fairly well until December 1941. She then became increasingly dyspneic following an episode of bronchopneumonia. The blood urea nitrogen was 42 mg per 100 cc and the maximum concentration of the urine was 1.016. Heart failure increased although digitalis and the restricted salt and fluid diet were followed. In April 1942 generalized anasarca developed. At this time mercurials in 2 cc doses were repeated at three to four day intervals. She soon returned to her household duties. The liver edge, however, remained 4 fingerbreadths below the costal border. Mercurials have been continued at four to five day intervals except for short periods when the patient refused treatment. Invariably during these lapses the edema of the abdominal wall and lower extremities quickly recur and dyspnea supervenes. With the resumption of therapy the condition again improved.

During the periods when the congestive heart failure was well controlled, her mental status was normal and she continued looking after her household duties. With the recurrence of heart failure she became disoriented and confused. When opiates were given during periods of increasing dyspnea she also became disoriented and once was comatose for twenty-four hours after being given only $\frac{1}{8}$ grain of morphine.

This case shows (1) that while digitalis is effective in controlling the early manifestations of heart failure, it is inadequate as heart failure becomes progressive, and (2) that mercurials have to be given at intervals adjusted to the clinical improvement shown. It is noteworthy that moderate renal insufficiency is no contraindication to the administration of mercurials.

Of interest in this patient is the action of small doses of opiates in the presence of cerebrovascular disease, resulting in periodic breathing, memory and judgment defects, and at times even coma, especially with increase in congestive heart failure. The opiates should be avoided in cardiac patients with advanced cerebrovascular disease and barbiturates used only as necessary.

CASE VII Congestive Failure Complicated by Severe Renal Insufficiency and Intolerance to Purine Compounds, and Severe Febrile Episodes—I. J. W., a forty year old attorney, has a diuresis of more than 3 liters following intravenous salyrgan given at three day intervals over a period of one and one-half years despite a urea clearance of 33 per cent and blood urea nitrogen of 60 mg per 100 cc. However, he shows untoward reactions to mercurial salts combined with theophylline, whether given intravenously, intramuscularly or by mouth.

His clinical course has been complicated by severe bronchopneumonic infections which have been treated with antibiotics and increased fluid intake. When the temperature rose to 102° F there were no restrictions made on the fluid intake. During one such episode the congestive heart failure was treated in the same manner as during the previous period when no fever was present. Diuresis following the mercurial was not as great as during the afebrile periods. During one other febrile episode the congestive heart failure did not increase and the mercurials were given at four to five day intervals because large amounts of water were lost sweating.

CASE VIII The Temporarily Mercury-fast Patient—P. B., a twenty-one year woman, had chorea and rheumatic carditis under treatment with salt-poor fluid-restricted diet, digitalis and an occasional dose of a mercurial for three years.

on account of heart failure. The response to the 2 cc. doses of mercurials at three to ten day intervals was 1 to $1\frac{1}{2}$ liters of urine or less. The response to each of two doses of 3 cc. and 4 cc. of mercurhydrin was a diuresis of 6 liters. She continued on the same dietary regimen and did not reaccumulate fluid so rapidly. Subsequently one cc. mercurhydrin given intravenously or intramuscularly at four to fourteen day intervals produced excellent diuresis.

This case shows that patients who cease to respond to ordinary doses of mercury (1 to 2 cc.) may respond to 3 cc. or 4 cc. It is not known why patients cease to respond to diuretics, possibly, improvement is brought about by decreasing the venous pressure in the abdomen, once diuresis starts, thus permitting increase in speed of blood flow through the glomeruli.

III Effects of Mercurials.—We have observed two deaths following the use of mercurials. Summaries of the cases follow.

CASE IX. H. A., forty-seven years of age, had hypertensive, arteriosclerotic heart disease for seven years and heart failure for two years. The first injection of silyrgan was followed by moderate diuresis. The second injection was followed by anuria for forty-eight hours, then oliguria for ten days and finally death from uremia.

CASE X. M. R., a sixty-eight year old man, hypertensive and diabetic, had anasarca of six months duration and recurring episodes of blurred vision. The heart was enlarged, rhythm was regular, blood pressure was 230/110. The fundi showed arteriovenous nicking and many soft and hard exudates and hemorrhages and slight papilledema bilaterally. Congestive heart failure and renal insufficiency with nitrogen retention became progressively more severe despite digitalization. In desperation a dose of mercupurin and aminophylline was administered. Twenty minutes later the patient died.

In the first case the ill effect was purely an unfortunate, unpredictable accident. With the thousands of injections given such an event is extremely rare and this small risk must be taken. The second case demonstrates the danger of the mercurials in extreme renal insufficiency. It is true, however, that in the presence of renal insufficiency severe congestive heart failure increases the abdominal venous pressure so as to make this insufficiency more severe, and startling improvement may follow the giving of a mercurial. Death which followed the intravenous injection of mercupurin and aminophylline may have been due to either drug or may even have been unrelated to the given therapy.

TREATMENT OF CONGESTIVE HEART FAILURE

General measures in the treatment of chronic congestive heart failure are to be discussed. These include rest, digitalis, diuretics, diet and fluid intake.

Rest.—Absolute bed rest has become the byword in the treatment of heart failure. It is regarded as the most important of all measures since it reduces the work of the heart. The word "rest" is a broad term

and one might ask what absolute bed rest is. Is it mental rest? Is it physical rest? How can it best be attained?

Rest should be long enough to attain maximum benefits. It should not be prolonged to the point where the patient rebels against it. It has been shown that excessive rest may be deleterious and harmful and defeat the purpose for which it is given.

While the patient is acutely ill it is not difficult to provide sufficient sedation to cause mental relaxation. This effect, along with the natural apathy of the acutely ill patient, will permit real physical and mental rest. However, once the patient recovers and finds himself imprisoned in his bed, he is inclined to ask "Is it worthwhile?" In most patients there certainly is no mental ease with protracted complete bed rest. In mild carditis or in recovery from uncomplicated myocardial infarction, particularly in the apprehensive individual, bed rest should be modified after the third or fourth week. The patient treated for chronic congestive heart failure need not be subjected to enforced bed rest since (1) bed rest alone will not clear up heart failure, and (2) vigorous diuresis will accomplish this result. The problem becomes a clinical equation. One must evaluate, on the one hand, the disturbance created by absolute bed rest and, on the other hand, the increased heart work caused by modified rest including some privileges out of bed.

As Dock¹ and Levine² have shown, enforced bed rest causes stagnation of blood in the dependent parts and increases the incidence of pulmonary embolism. In addition, Levine also showed that while the body is in the recumbent position fluid is shifted centrally from the periphery, burdening the right or left heart and causing an increase in pulmonary congestion and reduction in air space. When the left heart is already burdened, paroxysmal dyspnea and pulmonary edema may follow. The hemodilution with its decrease in serum protein may further increase this burden.^{2a}

Modified bed rest and later return to a sedentary occupation, though the heart failure has not cleared, is the most desirable method of treatment after a short period of complete bed rest. Patients should allow themselves more time for travel to and from work and take their lunches in their places of employment. The fluid and salt intake must be strictly controlled so that failure does not recur too quickly, and food intake should be controlled so that there is no gain in body weight. Rest periods should be insisted upon and may be taken by increasing the number of hours of bed rest at night and by resting in bed part of each week end.

We cannot be certain that in specific cases the increase in activity will not adversely affect the course of heart failure, nevertheless, modified bed rest appears to offer the patient great advantages, especially from the physiological and psychological aspects.

Digitalis.—Since Wuthering's day, digitalis bodies have been the mainstay in the treatment of congestive heart failure. Indeed, Christian³ is of the opinion that the existence of heart disease, not alone heart failure, is reason for the administration of digitalis. On the other hand, Lewis⁴ and others are of the opinion that digitalis is indicated only in the presence of a rapid ventricular rate with fibrillating auricles. Katz⁵ and his co-workers, however, insist that digitalis is of value in the prevention of recurrences of congestive heart failure, even in the presence of sinus rhythm. They agree that as the cardiac reserve is diminished, digitalis alone may no longer be effective. In the presence of Graves' disease, in infection, and in cardiac infarction, these observers feel that digitalis is not very effective.

Altschule and Runger⁶ and Stewart and Cohn observed that digitalis increased cardiac output. Friedman⁷ and his co-workers obtained no impressive results when digitalis was given in the presence of slow heart rates. Harrison⁸ and his co-workers found no definite relationship between heart failure and cardiac output.

Digitalis is of great value in the treatment of heart failure of all types and acts most dramatically in the presence of a rapid ventricular rate, especially with auricular fibrillation or flutter. When heart failure has its onset with auricular fibrillation accompanied by a rapid ventricular rate, digitalis acts by (1) increasing A-V nodal block and (2) increasing the work output per unit of oxygen of the ventricular fibers. Minute volume is thus increased along with a lessening of heart work. In the presence of sinus rhythm this drug acts by its direct effect on the efficiency of the ventricular fiber.

This direct effect on the efficiency of the ventricular fiber may chemically be similar to the effect of hypertrophy, for chemical analysis of heart muscle fiber after digitalization shows a diminution of potassium content as does the hypertrophied myocardial fiber.⁹ Apparently this loss of potassium from the cell fiber is in some manner associated with improved efficiency of oxygen consumption, as Harrison has suggested. Also interesting are the R-T and T wave depressions which follow digitalization and also hypertrophy which may be associated with this chemical change.

While digitalis should be given to every patient with heart failure, it will control only mild congestive failure, and early congestive failure that is not severe. Improvement from digitalis in regular rhythm is much less, and it is almost nil when the rate is slow.

It is agreed by most observers that digitalis is of little value in acute infections whether they are primarily cardiac or extracardiac. In fibrillation due to Graves' disease, digitalis is of little benefit. In failure associated with acute myocardial infarction and a rapid ventricular rate, full digitalization is often of great value, but in thyrotoxicosis,

pulmonary heart disease and constrictive pericarditis, results with digitalis are disappointing

In such cases too much time elapses before it is evident that digitalis is not too effective. Even in the presence of paroxysmal tachycardia or auricular fibrillation, the effectiveness of digitalis should not dissuade one from the use of diuretics at the same time even if failure is mild. Digitalis is best administered by mouth.

More recently purified glycosides have been favored. These preparations are given parenterally or by mouth. The value of a purified digitalis preparation is no greater than that of the average digitalis leaf except that (1) severe heart failure causes a decreased absorption of this drug from the intestinal tract and (2) a full digitalization dose may be given by the parenteral route without disturbing the very ill patient. Once the drug has shown its optimal effect the purified glycosides are of no greater value than the dried leaf. It has also been stated that the glycosides may be given in full digitalization dose by mouth without producing the usual toxic manifestation, and that these glycosides may be continued for longer periods of time without producing nausea. In our experience the incidence of nausea is no different when glycosides are given or when digitalis leaf is given, provided the administration of the drug is well supervised.

Strophanthus has been given intravenously in small doses in treatment of chronic heart failure when digitalis leaf was apparently not effective. Occasionally fair results have been observed. It is nevertheless preferable in such instances to administer the quicker acting glycoside such as digoxin or cedmalid rather than strophanthus because it is much less dangerous and the therapeutic effect at least as good.

Mercurials and Other Diuretics.—Mercury has been used as a diuretic for a long time as Fothergill's or Guy's pill containing 1 grain of mercury. Present day use of organic mercury compounds as diuretics started in 1920 when Saxl¹⁰ demonstrated the value of novasurol in heart failure. Since then the mechanism of mercury diuresis has been thoroughly investigated and established.

Blumgart¹¹ found that mercurials act by increasing blood volume, increasing glomerular filtration, and decreasing tubular reabsorption. Stewart¹² found a fall in blood specific gravity before diuresis occurs.

By studying the concentration of creatinine in plasma and urine, Schwartz¹³ has shown that salyrgan causes a decrease in tubular reabsorption.

It is common experience that once the heart has failed from progressive cardiac disease not precipitated by acute cardiac infarction or embolism, the patient becomes a chronic invalid. Digitalis is of limited value and is inadequate in the treatment of such failure, and the only drug that will maintain cardiac efficiency is the mercurial. Treatment should also include salt restriction, a low fluid

regimen and diuretics. The mercurials should be given with sufficient frequency to maintain fluid balance and prevent excessive accumulation of fluid and where a diuretic need be given care should be taken the mercurial should be given before the fluid is absorbed. It is also indicated when heart failure becomes a cause of edema.

Patients suffering from proteinuria, edema and anasarca should have an increasing output of urine. The diuretic should be given. When this precaution is not taken the edema may become extensive and distress is not infrequently caused. When a diuretic is omitted, urinary retention may occur and may be fatal.

The effectiveness of mercurial diuretics is diminished when the cardiac output is unusually low and when pleural effusion and ascites are present. Thus, it may be necessary first to evacuate the abdominal fluid and then follow with a mercurial. The reduction in intrathoracic pressure permits increased blood flow to the kidney and increased excretion of urine. Sometimes 5 to 10 cc. of 20 per cent decholin solution enhances the diuretic action of mercurials. Unless salyrgan is given the addition of xanthines is unnecessary since mercurial salts are combined with theophylline. Xanthines given alone are rarely effective and cause gastro-intestinal disturbances. They do not compare favorably with mercurials in diuretic effect.

In some instances the increase in the chloride ion permits a greater diuresis. Ammonium, calcium or potassium chloride should be taken for a period of two days before and on the day of the mercurial. When these salts are given the marked weakness associated with hypochloremia is lessened. Dosage varies but need not exceed 15 gm. per day. As a rule a dose of 3 gm. is sufficient.

Many patients do not tolerate continued administration of ammonium or potassium chloride on account of abdominal pain. Absorption does not always take place and a x-ray examination at times discloses the presence of many unabsorbed pellets of enteric-coated ammonium chloride tablets in the intestinal tract. In place of these salts 15 to 45 drops of dilute hydrochloric acid may be given two or three times a day for one or two days before the mercurial, or until the urine becomes acid. When given alone these salts are rarely effective though the ammonia is converted to urea. Urea as a 50 per cent solution* in doses of 15 cc. given three times a day is an effective diuretic when given alone or as an adjunct to the mercurial. The drug is objectionable because of its unpleasant taste. Also, large quantities of water must be taken with it. It does not cause profuse diuresis, but when well tolerated it is a safe maintenance diuretic.

* A 50 per cent solution of urea is made by dissolving 1 pound of the drug in 2 quarts of water.

Sometimes it may be necessary to give morphine when digitalis is not of immediate aid in improving progressive left ventricular failure such as may follow paroxysmal auricular fibrillation. The opiate allays acute anxiety and dyspnea and will, in some instances, bring about a cessation of the tachycardia. The mercurial may be given at the same time as the morphine is administered, or a short time later when the morphine effect is beginning to subside. Though the diuresis may not be as large because morphine depresses the diuretic effect, yet the mercurial is sufficiently effective so that the load of the heart is reduced.

Mercurials are indicated in congestive failure due to active rheumatic carditis. The response to digitalis is as poor as in other infections. In children with carditis liver enlargement usually precedes the development of other signs of congestive failure and persists after all other signs of failure have disappeared. Mercurials should be given as soon as the liver becomes enlarged, though the lungs remain clear. Digitalis should also be given, but should not be depended upon to combat failure. Clinical experience is that the better part of wisdom is to rely upon mercurials to control failure until carditis subsides when failure spontaneously improves.

Mercurials may be continued for indefinite periods and Scherf reports the administration of 600 to 700 injections over a period of twelve years.¹⁴ In some instances mercurials have been given daily for varying periods, but in most instances the interval has been three to five days.

The dosage varies with the particular needs of the case. One cubic centimeter should be given unless the diuresis which follows is too small. Most of our patients require from 1.5 to 2 cc. Occasionally a 0.5 cc. dose may be effective. It is, however, the exceptional patient who responds to this dose. The dose may be increased to 3 or even 4 cc. when 2 cc. is repeatedly ineffective. For the past six years one patient has been receiving 12 cc. intravenously per week in three injections. It is desirable that the dose be kept as small as possible. Some physicians in hospital practice have given 0.25 cc. daily for eight doses and claimed better results than with a single large injection. The method is impractical for home care and there is also objection to giving eight small injections because of the greatly increased danger of sloughing and infection. The total diuresis may, however, be enhanced by this method.

The intramuscular administration of the mercurials is safer than theavenous. The disadvantages are the severe pain and swelling which follow even the deep intramuscular injection. The irritation of the nerves present in the injected area sometimes causes
of the musculospiral and sciatic nerves, and occasional sloughs

For the intramuscular injection mercurial is the least purified of the mercurials.

The danger of mobilization of digitals during diuresis makes it advisable to omit digitals on the day of the injection.

The most common complaint of the patient receiving frequent injections of mercurials is the extreme dryness of the mouth and skin. This is due to excess loss of fluid from tissues which may or may not have been waterlogged, since mercurial diuresis is not selective.

Weakness, cramps in the legs and in the abdomen, unexplained spasm, fever and stupor less frequently follow mercurials and are very likely due to hypochloremia and excessive loss of fluids or excessive deprivation of the vitamin B group. In such patients the administration of smaller doses of mercurials may avoid the ill effects. When these symptoms are severe it may be necessary to allow 500 cc. of water and 2 to 3 gm. of salt to bring relief. The effects of giving vitamin B complex in a large series is yet to be observed.

Occasionally a macular rash followed by scaling is observed. Fortunately, this rarely occurs and sometimes does not reappear when the mercurial salt is changed. In one patient a rash appeared following the administration of every mercurial given, though diuresis was good. There were no other toxic manifestations and the mercurials are being continued.

Vomiting also occasionally follows mercurial diuretics. In two such cases the untoward effects were due to theophylline. When salyrgan was substituted for the salyrgan theophylline preparation the vomiting did not recur. In one patient with fever, delirium, disorientation and coma, the symptoms disappeared when salt and water were given.

When kidney impairment is present, mercurials may still be given in doses of 0.5 to 1 cc. One patient whose urea clearance is only 30 per cent still has an excellent response to the drug. When formed elements in the urine are due to stasis in the kidneys from congestive failure, diuresis is sometimes followed by lessening of albumin and formed elements. Even in the presence of red blood cells and cellular casts in the urine in subacute glomerular nephritis, when the need was desperate mercurials were given. In another patient who was waterlogged, mercurials remained effective for a short period. Though the routine use of mercurials in the presence of marked renal insufficiency with numerous red cells and cellular casts in the urine is not advised, two patients with moderate to severe kidney changes and heart failure are now ambulatory and comfortable on a three to five day mercurial regimen. When diuresis cannot be obtained by less drastic methods, mercurials should be tried.

Rarely death follows the administration of two or more doses of mercurials. DeGraff and Leluan¹⁶ have shown that death is caused

by action of these drugs on intraventricular conduction with terminal ventricular fibrillation or respiratory failure secondary Barker, Lindberg and Thomas¹⁶ mention depression of T waves, runs of extrasystoles, ventricular tachycardia and ventricular fibrillation causing death in dogs to whom mercurial salts were given intravenously Brown, Friedfeld, Kissin, Modell and Sussman¹⁷ report four fatal incidents following the use of intravenous mercurials In three of their four cases there had been untoward reactions to previous administration of mercupurin Kline and Seymour¹⁸ report death with anuria and oliguria following intravenous mercurial

Occasionally a mercury-fast patient may respond to 2 gm of theobromine, sodium salicylate or sodium acetate given by rectum or 6 gm of theocalcin by mouth One patient in failure has been maintained by this 6 gm dose during the past seven months

Fluids—Diet.—Should fluids be restricted or should they be given liberally? The orthodox treatment of congestive heart failure consists of depriving the patient of fluids On this regimen thirst and weakness are common complaints, especially after mercurial diuretics, since the daily salt intake is rarely below 5 gm This led Schroeder to permit a liberal intake of fluid, up to 4 liters a day in congestive failure with a diet containing 0.5 gm of salt a day With such low salt intake congestive heart failure responds to large fluid intake without need for mercurials as frequently as otherwise Schemm¹⁹ felt that if, in addition, an acid-ash diet were given to mobilize the sodium, such an increased fluid intake would enhance diuresis He realized that with limited fluid intake and with diminished cardiac output sufficient fluids are not provided to the kidneys for filtration He therefore gave large amounts of fluid so as to increase the amount of blood brought to the kidneys With this regimen, Schemm reports that patients no longer are thirsty despite marked loss of edema fluid Even in the presence of failure due to acute cardiac infarction, active myocarditis or severe nephritis, he reports excellent results with fluid intake up to 12 liters a day sometimes given in large part by the intravenous route Failure of this regimen is reported by Schemm in only 6 per cent of more than 400 patients with heart failure This work has great promise and may contribute much to the comfort of patients However, the difficulty in preparing a diet containing only 2 gm or less of salt is great. The taking of 4 or more liters of fluid a day is another hardship, and in larger amounts is even more trying Patients with edema resist the regimen since they are afraid to take large amounts of fluid. Salt-free food is difficult to obtain, for few commercial sources make it. In addition, the natural sodium content of many foods is high Our experience with this regimen confirms Schemm's report that an increased urinary output followed the increased fluid intake and the

acid ash diet. In severe congestive failure, however, urinary chloride output may be almost negligible after the first few days and rises only when diuresis follows the giving of a mercurial. When diuresis follows the giving of a mercurial, an output of 6 to 8 liters of urine is not uncommon. This total is made up of the usual output of 3 to 5 liters (when the intake is also 3 to 5 liters) and an additional 2 to 4 liters caused by the diuretic action of the mercury. Such an increase in urinary output is no greater than the diuresis which follows a mercurial when the ordinary salt-poor diet is being taken.

When considering fluid balance one must remember that the loss of fluid through extrarenal sources under normal circumstances may vary from 800 to 1500 cc. per day.²⁰ Thus, too strict fluid restrictions should be avoided in warm weather or in heated homes, since the fluid lost through the skin in such instances is more than normal. Also, during febrile periods, two factors must be constantly kept in view: (1) the marked increase in fluid lost through the skin may exceed urinary output and (2) the reduction in the food intake during febrile periods. The food allowed during afebrile states contains at least 1 liter of fluid. This liter of fluid added to the 1200 to 1500 cc. ordinarily permitted makes the fluid intake at least 2000 to 2500 cc. per day. Since skin evaporation is increased during febrile periods and food intake is reduced, the fluid allowed may be further increased, the total depending upon the extent of the rise of temperature. In most instances short periods of mild to moderate infections may not intensify severity of heart failure. Frequently profuse perspiration causes a loss of fluid which may exceed the urinary output. In one such instance the bedclothes were drenched many times during the day and the congestive heart failure actually diminished during the course of bronchopneumonia. On the other hand, in other instances congestive heart failure increases during severe infections and must be treated by mercurials.

Kempner²¹ prescribed a diet for hypertension consisting of rice, sugar, fruit and fruit juices with vitamin and iron supplements containing 2000 calories. Again this regimen is difficult to follow and patients object to its continuation for a prolonged period. The virtue of this diet is the low sodium content, 0.25 to 0.45 gm., and the low protein content.

Likewise, the modified Karell diet is really a salt-poor, neutral to acid ash, fluid restricted diet. The total intake is about 1200 cc. when the ordinary output is about 2000 cc. This output includes urine, insensible perspiration, vapor lost through the lungs, and the fluid lost through the stool. The excess output over intake is made up by the release of edema fluid.

CONCLUSION

Chronic congestive heart failure is an indication for mercurials as well as digitalis therapy. Experience has shown that the indications for each are the following. For *digitalis*—(a) mild failure and (b) principally for the maintenance of a slow ventricular rate in auricular fibrillation. For *mercurials*—(a) as a maintenance diuretic in prolonged failure not adequately controlled by digitalis, (b) in preventing attacks of paroxysmal dyspnea and pulmonary edema, especially when associated with a critical weight level, (c) in right heart failure with persistent hepatic enlargement, for additional hepatic enlargement or other signs of heart failure, (d) in pulmonary vascular congestion and increasing reduction in air space from pulmonic stasis to prevent subsequent invalidism and (e) to clear failure earlier so as to permit earlier ambulation.

The dosage of mercury is 1 to 2 cc, though occasionally 4 cc are required. The regular dose may be repeated at twenty-four hour intervals when failure remains acute.

The only contraindications to mercury are (1) acute nephritis and (2) severe chronic renal disease, practically pre-uremia. Sensitivity to mercury is unpredictable and rare. A patient may be sensitive to one preparation but tolerate others. The intramuscular route is the safest.

On a salt-free diet cardiac patients tolerate liberal amounts of fluids. On a salt-poor diet, however, fluids should be restricted to 1200 to 1500 cc per day. In febrile states fluids should be given more liberally, depending upon the temperature. The same principle applies to warm weather or heated homes.

Complete bed rest is indicated during the acute phase of heart failure, during the first three weeks of uncomplicated cardiac infarction, and in moderate to severe carditis. Thereafter bed rest should be modified.

Chronic congestive heart failure may be treated effectively at home. The patient may be ambulatory and continue in a sedentary occupation. Such a regimen has great social value, for it keeps the patient in his place in society and bolsters his morale.

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